Rheumatoid Arthritis, as a Clinical Disease, but Not Rheumatoid Arthritis-associated Autoimmunity is Linked to Cardiovascular Events

Helene Gouze (helene.gouze@aphp.fr)
Hôpital Ambroise-Pare https://orcid.org/0000-0002-5333-0316
Philippe Aegerter
Department of Public Health and Biostatistics, UMR1168, INSERM/UVSQ-Paris Saclay University, France
Roula Said-Nahal
Ambroise Paré University Hospital: Centre Hospitalier Universitaire Ambroise Pare
Marie Zins
Population-based Cohorts Unit UMS 011, Paris University, Villejuif, France
Marcel Goldberg
Population-based Cohorts Unit UMS 011, Paris University, Villejuif, France
Guillaume Morelle
Ambroise Paré University Hospital: Centre Hospitalier Universitaire Ambroise Pare
Georg Schett
Friedrich Alexander University Erlangen Nuremberg: Friedrich-Alexander-Universitat Erlangen-Nurnberg
Maxime Breban
Ambroise Paré University Hospital: Centre Hospitalier Universitaire Ambroise Pare
Maria-Antonietta D'Agostino
Università Cattolica del Sacro Cuore: Universita Cattolica del Sacro Cuore

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Abstract

Background: Rheumatoid Arthritis (RA) is characterized by increased cardiovascular (CV) mortality. CV events are particularly high in patients with RA-specific autoimmunity, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), raising the question whether RA-specific autoimmunity itself is associated with CV events.

Methods: New CV events (myocardial infarction, stroke or death by CV cause) were recorded in 20,625 subjects of the Electricité de France – Gaz de France (GAZEL) cohort. Self-reported RA cases in the GAZEL cohort were validated by phone interview on the basis of a specific questionnaire. In 1,618 subjects, in whom serum was available, RF and ACPA were measured. A piecewise exponential Poisson regression was used to analyze the association of CV events with presence of RA as well as RA-specific autoimmunity (without RA).

Results: CV events in GAZEL were associated with age, male sex, smoking, hypertension, hyperlipidemia and diabetes mellitus (HR from 1.06 to 1.87, $p < 0.05$). Forty-two confirmed RA cases were identified. Confirmed RA was significantly associated with CV risk increase (HR of 3.03; 95% CI: 1.13-8.11, p=0.03) independently of conventional CV risk factors. One hundred seventy-eight subjects showed RF or ACPA positivity without presence of RA. CV events were not associated with ACPA positivity (HR: 1.52, 95% CI: 0.47-4.84, p= 0.48) or RF positivity (HR: 1.15, 95% CI: 0.55-2.40, p= 0.70) in the absence of RA.

Conclusions: RA, as a clinical chronic inflammatory disease, but not mere positivity for RF or ACPA in the absence of clinical disease is associated with increased CV risk.

Introduction

Rheumatoid Arthritis (RA) is an autoimmune chronic inflammatory disease characterized by synovitis leading to joint destruction and functional impairment (1). Prevalence of RA is around 0.5% in Caucasian population (2). RA development is promoted by a combination of genetic susceptibility and environmental factors that leads to breech of immune tolerance and formation of autoantibodies such as Rheumatoid Factor (RF) and Anti-Citrullinated Peptide Antibodies (ACPA) (1). Autoimmunity precedes RA by several years (positive predictive value > 96% at 5 years) (3–5) and is associated with higher disease activity and structural damage (6, 7).

RA is characterized by an increased morbidity and mortality (8–11). Besides structural damage and its consequences on disability, increased cardiovascular (CV) risk, including myocardial ischemia and heart failure, has been described in RA (10). Aside from the consequences from disability and infections, CV disease is responsible for increased mortality in RA (8–11). Increased CV risk in RA does not only seem to be explained by standard CV risk factors, but also by chronic inflammation, which accelerates the process of atherosclerosis (12, 13). This process seems to be independent from the use of concomitant treatments such as corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs), which also add to CV risk (14).

In recent years, several studies suggested that RA with positive RF and/or ACPA presents a higher CV risk (9, 15–18). Thus, one may think that RF and ACPA could influence CV risk independently from RA. However, evidence that CV disease may be linked to the presence of autoantibodies, independent from the occurrence of RA, is scarce, and only one study suggested that autoimmunity increases CV risk (15, 16, 19) in a subpopulation of African-American women, but not in all women with positive autoantibodies (19). To try to explore this question, we made use of a large epidemiological cohort study (20–22) and separately tested the influence of RA on CV risk as well as the impact of autoantibodies (RF/ACPA) without presence of RA on CV risk.

Methods

Study population

The GAZEL cohort was started in 1989 and included 20,625 current employees at that time of the French national company of services named “Electricité de France – Gaz de France” (20, 21). Women were aged between 35 and 50 years and men between 40 and 50 years at inclusion, respectively. Demographic characteristics and a complete medical history were recorded in all subjects at baseline. Thereafter, subjects received an annual questionnaire covering information on a large spectrum of pathologies, including rheumatic and musculoskeletal diseases (RMDs) as well as CV risk factors (20, 21). In addition, plasma was collected from a fraction of the GAZEL cohort between 2000 and 2005. In 2010, a specific screening questionnaire dedicated to identify patients affected with inflammatory joint disorders, including RA, was included in the GAZEL workup.

The GAZEL protocol was approved by the French authority for data confidentiality (‘Commission Nationale Informatique et Liberté’) and by the Ethics Evaluation Committee of the ‘Institut National de la Santé et de la Recherche Médicale (INSERM)’ (IRB0000388, FWA00005831).

RA diagnosis ascertainment

All subjects who declared to suffer from RA in the 2010 screening questionnaire were included in the procedure. After having accepted to be contacted, patients were reached by phone and interviewed by an experienced rheumatologist trained for this purpose using a phone questionnaire specifically developed for ascertaining the diagnosis of RA (See Additional file 1). This questionnaire had first been validated on a panel of 102 consecutive outpatients consulting for any rheumatic disease (including RA, axial spondyloarthritis or psoriatic arthritis) in the Rheumatology Department of Ambroise Paré Hospital (Boulogne-Billancourt, France). The questionnaire was administrated by a physician blinded to the patients’ diagnosis and its sensitivity and specificity for the diagnosis of RA were estimated to 100% and 89%, respectively (See Additional file 1).

ACPA and RF determination

Aliquots of plasma stored at -80°C were used to quantify the presence of ACPA and RF antibodies. Laboratory tests were realized in a specialized research laboratory (Department of Immunology and

Internal Medicine, University of Erlangen-Nuremberg) and consisted in IgG ACPA ELISA (Reference Euroimmun EA 1505–9601 G) and IgM-RF ELISA (Reference IBL International RE70341). Cut-off value for ACPA was defined as positive if ≥ 4.6RU/mL, and for RF if ≥ 10U/mL.

Statistical analysis

Clinical and biological parameters (age, sex, CV risk factors, including high blood pressure, smoking habit, alcohol intake, obesity, diabetes, dyslipidemia, death), and the occurrence of CV events, including myocardial ischemia, non-lethal stroke, and death due to CV cause were reported using descriptive statistics (mean and standard deviation or median and interquartile range). The outcome variable was the occurrence of new CV event, including non-lethal myocardial ischemia, non-lethal stroke or death due to CV disease. Explanatory variables were multiple and concerned RA, autoantibodies (ACPA and RF) and already known CV risk factors. Cut-off values defining risk factors were considered as follows: presence of obesity if body mass index (BMI) ≥ 30, alcohol intake if ≥ 14 glasses per week for women and ≥ 21 glasses per week for men, tobacco consumption if number of pack-years (PY) ≥ 20. Family history of myocardial infarction was considered when it occurred before the age of 60 years (mother) or 50 years (father). As blood samples were collected between 2000 and 2005 and death causes were available until 2014, the analysis concerned the occurrence of new CV events from 2005 to 2014. We used piecewise exponential Poisson regression, as the data were composed of discrete times of observation (23). High blood pressure, dyslipidemia, diabetes, BMI, tobacco and alcohol intakes were accounted as time-dependent covariates. Subjects who declared having RA but who were not reached by phone to confirm their diagnosis were excluded from the analyses. A sensitivity analysis was performed to compare subjects with available plasma sample and subjects without.

Results

Identification of CV events

GAZEL cohort enrolled 20,625 subjects, including 5,614 women (27.2%) and 15,011 men (72.8%). Mean ± SD age at inclusion was 44.2 ± 3 years. Characteristics of the cohort at the beginning of the analysis period (2005) are reported in Table 1. From 2005 to 2014, a mean of 169 CV events occurred every year in the whole cohort. During this observation period, 1,687 subjects in the whole cohort presented a new CV event, 129 of them were lethal and 1,558 not lethal.

Table 1
Demographic and clinical characteristics of GAZEL subjects in 2005

Variable	Global cohort (N = 19,557)	Non-collected* subjects (N = 17,939)	Collected* subjects (N = 1,618)
Mean age (years)	60.2 ± 3.49	60.1 ± 3.51	60.6 ± 3.25
Sex (% men)	72.4% (71.7–73%)	71.5% (70.8–72.1%)	82.1% (80.1–83.9%)
Mean retirement age (years)	55.3 ± 3	55.3 ± 3.1	55.4 ± 2.6
GAZEL 2005 questionnaire response rate	74% (73.4–74.7%)	72% (71.3–72.6%)	97% (96-97.7%)
CV risk factors			
Hypertension	17.3% (16.8–17.9%)	17.1% (16.6–17.7%)	19.4% (17.5–21.4%)
Diabetes	4.1% (3.8–4.4%)	4.1% (3.8–4.4%)	4.4% (3.5–5.6%)
Hyperlipidemia	20.5% (19.9–21%)	19.8% (19.3–20.4%)	27.2% (25-29.4%)
Family history of myocardial infarction	6.5% (6.1–6.8%)	6.4% (6-6.8%)	7.2% (6 -8.6%)
Body mass index	26 ± 3.7	26 ± 3.7	25.6 ± 3.3
Smoking (% ≥20 pack-years)	23.2% (22.6–23.7%)	23.4% (22.8–24%)	20.1% (18.2–22.2%)
Alcohol consumption % ≥ to 21 glasses/week (men) % ≥ to 14 glasses/week (women)	13.1% (12.6–13.6%)	12.6% (12.1–13.1%)	18.5% (16.7–20.5%)
CV events			
All events	1.7% (1.5–1.8%)	1.7% (1.5–1.9%)	1.3% (0.8-2%)
Stroke	0.5% (0.4–0.6%)	0.5% (0.4–0.6%)	0.4% (0.1–0.8%)
Myocardial infarction	1.2% (1-1.3%)	1.2% (1-1.4%)	0.9% (0.5–1.5%)

**Collected subjects: those with available blood sample for ACPA/RF testing. Results are expressed as mean (standard deviation) or percentage (95%CI)*

(This table should appear at the beginning of the results part).

Identification of RA patients

From the 18,752 subjects still followed in 2010, year in which the questionnaire on RMDs was administrated, 13,960 replied to that questionnaire. 421 subjects defined themselves to have RA. Of these 421 subjects, 197 were reached by phone and RA diagnosis was confirmed in 42 and dismissed in 155 of them (See flowchart Fig. 1). Among 42 confirmed RA, 30 were men and 12 were women with a mean ± SD age of 61.2 ± 3.4 years. Median RA duration was 9 years (range: 1–43 years). There was no significant difference at baseline between RA patients and the whole cohort (in 2005).

Among RA patients, 13 had an available plasma sample. Treatment information was available for 30 of them: 87% received at least one disease modifying anti-rheumatic drug (DMARD) (26/30). Among them, 69% had only conventional synthetic DMARDs (18/26), 8% had only biological DMARDs (2/26) and 23% received both (6/26). Patients treated with corticosteroids represented 30% (9/30 patients), 78% of them took < 8 mg per day of prednisone.

Association between RA and CV events

RA was significantly associated with an increased incidence of CV events in both univariate and multivariate analyses, with a hazard ratio (HR) of 3.03 (95% CI: 1.13–8.11, p = 0.03, multivariate analysis) (Table 2). CV events were also associated with established CV risk factors, such as male sex (HR: 1.87, 95% CI: 1.5–2.34, p < 0.001), tobacco consumption (HR: 1.54, 95% CI: 1.31–1.80, p < 0.001), high blood pressure (HR: 1.51, 95% CI: 1.30–1.76, p < 0.001), diabetes (HR: 1.25, 95% CI: 1.00-1.56, p = 0.05), dyslipidemia (HR: 1.19, 95% CI: 1.03–1.38, p = 0.02) and age (HR: 1.06, 95% CI: 1.04–1.09, p < 0.001), but not obesity, which was found significantly associated only in the univariate analysis (HR: 1.49, 95% CI: 1.24–1.79, p < 0.001). In contrast, alcohol consumption was protective, with an HR of 0.72 (95% CI: 0.58–0.88, p = 0.001).

Table 2
Independent association between rheumatoid arthritis (RA) and incidence of cardiovascular events in the whole GAZEL cohort

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	p
Confirmed RA	**3.11 (1.17–8.32)**	**0.02**	**3.03 (1.13–8.11)**	**0.03**
Gender (male)	**2.37 (1.92–2.94)**	**< 0.001**	**1.85 (1.50–2.34)**	**< 0.001**
Tobacco consumption (≥ 20 PY)	**1.84 (1.58–2.15)**	**< 0.001**	**1.54 (1.31–1.80)**	**< 0.001**
High blood pressure	**1.78 (1.54–2.06)**	**< 0.001**	**1.51 (1.30–1.76)**	**< 0.001**
Diabetes	**1.72 (1.39–2.13)**	**< 0.001**	**1.25 (1.00-1.56)**	**0.05**
Dyslipidemia	**1.40 (1.21–1.62)**	**< 0.001**	**1.19 (1.03–1.38)**	**0.02**
Obesity (BMI ≥ 30)	**1.49 (1.24–1.79)**	**< 0.001**	1.17 (0.97–1.43)	0.11
Parental antecedent of myocardial infarction	1.17 (0.93–1.47)	0.18	1.11 (0.88–1.40)	0.37
Age (years)	**1.09 (1.07–1.12)**	**< 0.001**	**1.06 (1.04–1.09)**	**< 0.001**
Alcohol consumption	**0.83 (0.68–1.02)**	**0.07**	**0.72 (0.58–0.88)**	**0.001**
Analysis consisted in piecewise-exponential Poisson regression to assess longitudinal data from 2005 to 2014.				
(This table should appear in results part next to the session “Association between RA and CV events”).				

Identification of autoantibody-positive individuals

Plasma samples were available in 1,618 subjects of the GAZEL cohort. As compared to the non-collected cohort, collected subjects had a similar prevalence of CV events including stroke and myocardial infarction. Also CV risk factors were comparable between non-collected and collected subjects. Only dyslipidemia and alcohol consumption were slightly higher in the collected subjects (Table 1). With respect to the RA validation questionnaire, 9 RA patients were identified among the collected subjects. Besides, 179 (11.1%) of the 1,609 collected subjects without RA had either positive ACPA or RF (N = 8), ACPA only (N = 37) or RF only (N = 134). All 9 RA patients were autoantibody positive (N = 8 ACPA + RF+; N = 1 ACPA+).

Association between RA-specific autoantibodies and CV events

The association between ACPA and CV risk was studied in non-RA subjects who had positive ACPA and/or RF (N = 179). No association was observed between the occurrence of CV events and ACPA positivity in those subjects (HR: 1.52, 95% CI: 0.47–4.84, p = 0.48, multivariate analysis) (Table 3).

Similarly, no association was observed between RF positivity and CV events (HR: 1.15, 95% CI: 0.55–2.40, p = 0.70).

Table 3
Association of ACPA or RF positivity (without RA) with incident CV events in subjects with stored serum

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Presence of ACPA	2.07 (0.84–5.11)	0.12	1.52 (0.47–4.84)	0.48
Presence of RF	1.55 (0.49–4.90)	0.46	1.15 (0.55–2.40)	0.70
Other factors				
Gender (male)	1.86 (0.90–3.87)	0.09	1.20 (0.57–2.55)	0.63
Age (years)	**1.17 (1.09–1.26)**	**< 0.001**	**1.14 (1.06–1.23)**	**< 0.001**
High blood pressure	**2.19 (1.40–3.42)**	**< 0.001**	**1.87 (1.17–2.96)**	**0.008**
Diabetes	1.26 (0.55–2.90)	0.59	0.84 (0.35–2.01)	0.70
Dyslipidemia	1.57 (1.01–2.45)	0.50	1.42 (0.90–2.24)	0.13
Obesity (BMI ≥ 30)	1.14 (0.57–2.29)	0.71	0.87 (0.42–1.78)	0.70
Tobacco consumption (≥ 20 PY)	**2.21 (1.39–3.50)**	**< 0.001**	**1.87 (1.16–3.02)**	**0.01**
Alcohol consumption	0.91 (0.51–1.62)	0.75	0.78 (0.43–1.39)	0.39
Parental antecedent of myocardial infarction	1.01 (0.47–2.20)	0.97	0.85 (0.39–1.86)	0.69
This analysis only concerned the collected subjects (i.e. those with available blood sample for ACPA/RF testing), without RA (N = 1,609)				
(This table should appear in results part next to the session “Association between RA-specific autoantibodies and CV events”).				

Discussion

This study shows that RA, as a clinical disease, but not RA-related autoimmunity is associated with CV events. It is known that RA is associated with two-fold increased risk for CV disease compared to the general population (24–26). While the overall CV risk in RA patients is based on traditional risk factors as well as immune changes related to RA, the excess risk of RA is usually considered to be based on increased inflammation and/or autoimmunity (24). While elevated systemic markers of inflammation have shown to be associated with a higher CV risk (27), other studies have also reported that CV risk is higher in RA patients with positive ACPA (15–18), but such observation could be related to the severity of

RA correlating with ACPA positivity (28), rather than to an independent association with ACPA. Hence, disentangling the effect of autoimmunity from the one of inflammation on CV risk in RA population is difficult, if not impossible.

The fact that ACPA and RF positivity precedes RA and that some individuals are positive for RF or ACPA without even developing the disease allows to separately assess the role of RA-related autoimmunity and RA, as an inflammatory joint disease, on CV risk (4–6). The analysis of GAZEL individuals that were positive for RF and/or ACPA permitted to directly evaluate the association between ACPA/RF and CV without the influence of arthritis. This analysis clearly showed that RA-related autoimmunity is not associated with an increased risk for CV disease, indicating that systemic inflammation is required for precipitating CV events. Hence, it is conceivable that effector function of autoantibodies, i.e. Fc- mediated cytokine release, which translates asymptomatic autoimmunity to inflammatory disease is critical for conveying CV risk (29).

In the GAZEL cohort, traditional risk factors such as male sex, age smoking, hypertension, hyperlipidemia and diabetes mellitus were independently associated with CV events. Notably, presence of RA was significantly associated with CV disease with a hazard ratio of 3.0. The strength of the association between CV events and RA is reflected by the fact that the number of ascertained RA cases was rather low in this cohort but nonetheless this association was robust. This observation also supports the robustness of the lack of association between autoantibodies and CV risk as the numbers of autoantibody positive subjects was much higher than the one with RA. The overall low number of ascertained RA cases can be explained by the fact that participants of the GAZEL cohort were mostly males (> 70%). Considering a prevalence of RA of 0.5% in the French population (2), that only up to 1/3 of RA patients being males and that not all subjects with self-reported RA could be validated, the numbers of observed and established RA cases fits the numbers of expected RA cases.

Strength of this study includes the fact that the increased risk of CV events in RA patients as compared to controls was confirmed in the same cohort and that also the associations between RA and CV events on one hand, and autoantibodies and CV events in the other were assessed in the same cohort. Another strength is that the ascertainment of RA cases did not rely merely on self-reporting but was confirmed by experienced rheumatologist, using a dedicated questionnaire that was developed and validated for this purpose. The only study which assessed the association between both ACPA and RF in non-RA patients is the one demonstrating that the presence of autoantibodies was associated with CV risk increased in African American women, and the diagnosis of RA was based on self-reporting information (19). Limitations are the fact that plasma was not available in the entire GAZEL cohort and hence autoantibody data were only obtained in a fraction of the cohort. On the other hand, subjects with plasma did not essentially differ from the others with respect to demographic characteristics, CV risk factors and CV events. Furthermore, the robustness of a lack of association between autoantibodies and CV events is supported by the fact that positive association could be observed for RA, despite the number of RA cases was substantially lower than the number of subjects positively tested for autoantibodies.

Conclusion

These data show that CV risk in RA is dependent on the inflammatory disease itself, while the mere presence of RA-related autoimmunity is not associated with CV disease. Thus the higher risk for CV events in autoantibody-positive RA is likely related to a more severe and chronic course of the disease rather than direct effects of autoantibodies on the vessels. These data support the observations that effective control of inflammation may lower CV risk (30, 31).

Abbreviations

ACPA: Anti-Citrullinated Peptide Antibodies

CV: Cardiovascular

DMARDs: Disease Modifying Anti-Rheumatic Drugs

RA: Rheumatoid Arthritis

RF: Rheumatoid Factor

Declarations

Ethics approval and consent to participate

The GAZEL protocol was approved by the French authority for data confidentiality (‘Commission Nationale Informatique et Liberté’) and by the Ethics Evaluation Committee of the ‘Institut National de la Santé et de la Recherche Médicale (INSERM)’ (IRB0000388, FWA00005831).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Cohortes team of the Unit UMS 011 Paris University - Inserm - Versailles St-Quentin-Paris-Saclay University but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Cohortes team of the Unit UMS 011 Paris University - Inserm - Versailles St-Quentin-Paris-Saclay University responsible for the GAZEL database management.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

HG, PA, MB and MADA analyzed and interpreted the data and drafted the manuscript. GS performed the autoantibodies quantification, contributed to data interpretation and manuscript writing. GM and RSN performed the validation process of diagnosis. MZ and MG are responsible for the GAZEL database management and contributed to data interpretation and manuscript writing. All authors contributed, read and approved the final version of the manuscript.

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Figures

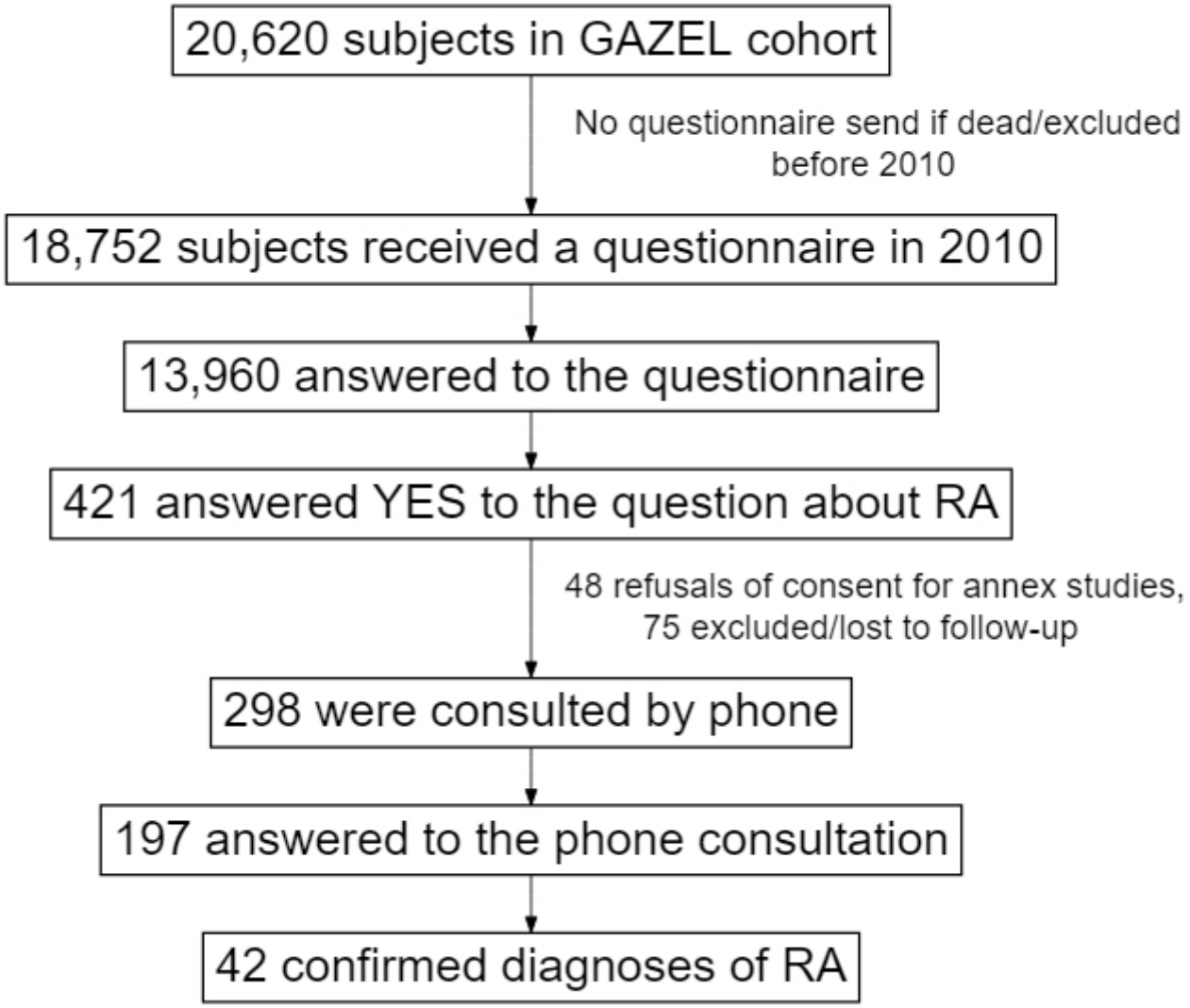

Figure 1

Flowchart of the rheumatoid arthritis (RA) diagnosis confirmation process

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