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Long-Term Residential Ambient Air Pollution and Rheumatoid Arthritis: A Systematic Review

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Abstract

Background: There has been increasing interest regarding the effects of air pollution on the risk of rheumatoid arthritis. Unfortunately, epidemiologic research on air pollution effects remains scant and offers conflicting results.
Objectives: This study aimed to systematically review the epidemiologic literature on RA morbidity due to long-term residential air pollution.
Materials and Methods: The authors independently carried out searches in MEDLINE and EMBASE through June 2015 (1974 - 2015). The searches were limited to English, Spanish and Russian. To complement the search strategy, authors and experts in the field were contacted, and hand-searches were carried out for articles included in reference lists. Peer-reviewed epidemiologic studies were eligible only if they explored the risk for RA in adults associated with air pollution exposure. Studies were omitted if they relied on self-report alone, experimental studies, short-term effects of air pollution, juvenile arthritis, or other autoimmune rheumatic diseases. Two authors independently extracted information about study characteristics. The study's quality was assessed with the Newcastle-Ottawa scale.
Results: Four relevant papers were included in a qualitative synthesis. Two studies showed significantly higher risks for RA in people living within 50 m of a heavy traffic road. No firm conclusions could be made for particulate matter. In one study, NO_2 was associated with seronegative RA among smokers. The risk for SO_2 was significant in one study. In the only relevant study, O_3 was linked to RA.
Conclusions: Proximity to road traffic might be a risk factor for RA as there are suspected effects associated with NO_2 and SO_2. Overall, the available evidence is too preliminary and scarce to draw firm conclusions. However, the results indicate the feasibility of further studies elucidating on the relationship between air pollution and RA.

Keywords: Arthritis, Rheumatoid, Air Pollution, Particulate Matter, Nitrogen Dioxide, Sulfur Dioxide, Ozone

1. Context

Rheumatoid arthritis (RA) is the most common chronic systemic autoimmune disease; it affects the joints, musculoskeletal apparatus, and connective and fibrous tissues (1, 2). Depending on the concomitant presence/absence of two specific autoantibodies - anti-citrullinated peptide antibody (ACPA) and rheumatoid factor (RF) - seropositive and seronegative types of RA can be discerned (3). The prevalence of RA is estimated at 0.3% - 1% with an onset between 20 and 40 years of age and higher incidence in women (2). RA leads to considerable physical and social disability and decreased life expectancy, with cardiovascular, infectious, hematological, gastrointestinal and pulmonary complications representing the main causes of premature mortality (4, 5). Expressed as disability-adjusted life-years, its global burden has actually increased since 1990, from 3.3 million to 4.8 million in 2010 due to the population trends observed in modern societies (6).

RA is a multifactorial disease with pathogenesis characterized by a complex interplay between genetic and environmental factors. The former account for about 60% of the risk, leaving an important role for the latter (5, 7). Smoking is a well-established and pivotal risk for RA, especially among seropositive individuals; occupational silica exposure might also be held accountable (7, 8). There is increasing evidence that air pollution might promote the onset of RA on its own (7, 8). The key culpable pathways include systemic inflammation, consecutive release of inflammatory cytokines, promotion of oxidative stress, and altered immune response leading to the production of autoantibodies and autoimmune reactions (8). Unfortunately, epidemiologic research on air pollution effects remains scant and presents conflicting results. In cases of controversial findings on urgent topics of international interest, a systematic evaluation of the literature is war-

ranted in order to contrast existing evidence, highlight and identify reasons for discord, and present a higher level of data synthesis that can be used to reconcile these disparities.

This study aimed to systematically review the epidemiologic literature on RA morbidity due to long-term residential air pollution.

2. Evidence Acquisition

2.1. Data sources and study selection

This systematic review follows the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) guidelines (9). An a priori review protocol and data extraction forms were developed. Two of the authors independently carried out electronic searches in MEDLINE (PubMed) and EMBASE (ScienceDirect) through June 2015 with no timeframe restrictions (1974 - 2015). We used combinations of the following free-term keywords: "air pollution", "particulate matter", "$PM_{2.5}$", "NO_2", "traffic", and "rheumatoid arthritis". The searches were limited to English, Spanish, and Russian. In ScienceDirect, the following filters were applied: journal, rheumatoid arthritis, autoimmune disease, immune system, immune response, oxidative stress, air pollution, nitric oxide, and rheumatoid arthritis. Articles were screened through three stages: titles, abstracts, and full texts. Duplicate publications were excluded. Peer-reviewed epidemiologic studies were eligible only if they explored the risk for RA in adults associated with air pollution exposure. Studies were omitted if they relied on self-report alone, experimental studies, short-term effects of air pollution, juvenile arthritis, or other autoimmune rheumatic diseases. To complement the search strategy, authors and experts in the field were contacted, and hand-searches were carried out for articles included in reference lists.

2.2. Data Extraction

For further processing, information was extracted and stored regarding study design, settings, exposure as well as outcome assessment, population, data analytic strategy, and results. Different objective indicators of air pollution exposure were of potential interest, such as gaseous contaminants, particulate matter, proximity to major roads, and traffic intensity at the residential address. RA status had to be determined according to objective and valid criteria, not simply by self-reported diagnosis. Individual study quality was assessed with the Newcastle-Ottawa scale (NOS) for cohort and case-control studies (10). Studies scoring $\geq$ 8 out of 9 "stars" were considered to be of high quality. At all stages, inter-rater disagreements were resolved through consensus and consultation with a third reviewer.

A quality effects meta-analysis (11, 12) was intended in the review protocol, but it was not feasible due to the low number of included datasets per air pollution indicator as well as the incompatible effect sizes and designs across studies; therefore, only qualitative synthesis was performed.

3. Results

3.1. Literature Search Results

We carried out electronic searches in PubMed and ScienceDirect (filters: journal, rheumatoid arthritis, autoimmune disease, immune system, immune response, oxidative stress, air pollution, nitric oxide, and rheumatoid arthritis), identifying 180 and 331 records, respectively. After duplicates were removed, we screened the remaining 475 records; after further removing 469 records that failed to meet inclusion criteria, we selected 6 for full-text reading. Of those, 2 more were eliminated: Bernatsky et al. (13) and Zeft et al. (14). The former reported results for autoimmune rheumatic diseases in general without stratification, while the latter focused on juvenile idiopathic arthritis. No additional articles were retrieved after handsearching the reference lists of articles already included. Figure 1 presents a flow diagram of the electronic search strategy.

3.2. General Description of the Studies

Table 1 illustrates the baseline characteristics of included studies. Four articles reported results based on three distinct cohorts - the Border Air Quality Study carried out in British Columbia (15) the Nurses' Health Study (NHS) in the United States (16, 17) and the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) in Sweden (18). The relationship between air pollution and RA was based on a cohort design in Hart et al. (17) and Hart et al. (16) a nested case-control study in De Roos et al. (15) and a population-based case-control study in Hart et al. (16). The analyzed sample sizes ranged from 1497 cases and 2536 controls in the EIRA study to 640,041 participants (1911 to 3333 cases depending on case definition) in the Border Air Quality Study. Overall, the sample sizes were satisfactory. The cohorts comprised mostly middle-aged people. In the EIRA study, women represented $\approx$ 70% in both cases and in the controls. In the Border Air Quality Study, they comprised about half of the participants. Finally, due to its nature, the NHS dataset contained only women.

The assessment of RA cases adhered to valid and objective criteria in all studies. In the NHS, a self-reported doctor-diagnosis was followed by inspection of participants' medical records in order to ensure their RA status.

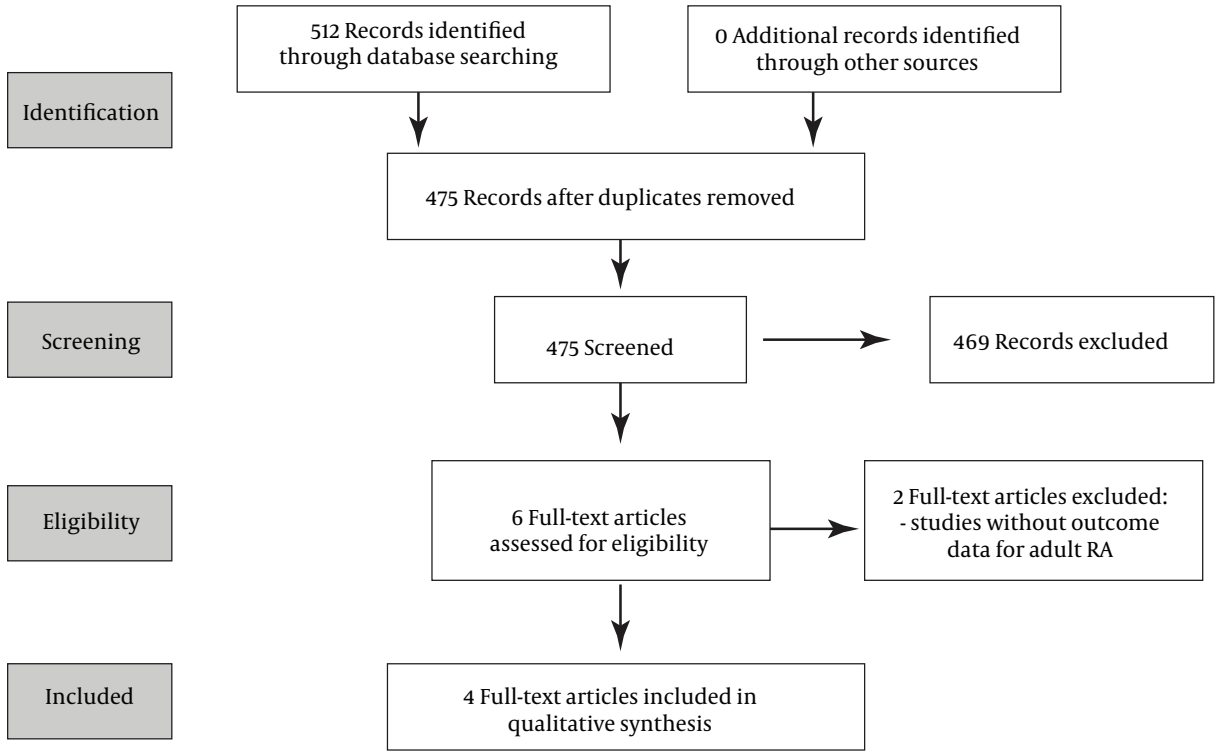

Figure 1. PRISMA Flow Diagram Describing the Study Selection Process

In the EIRA, the researchers relied on rheumatologist examination and, similar to the NHS, classified their cases according to the American college of rheumatology 1987 diagnostic criteria. Interestingly, De Roos et al. (15) used three different RA definitions: $\geq$ 3 ICD-9 codes for RA (RA-ICD-9); $\geq$ 2 codes and $\geq$ 1 prescriptions for a disease modifying antirheumatic drug or steroids (RA-prescription); and $\geq$ 2 codes and $\geq$ 1 for a visit to a physician specialist (RA-specialist). With the exception of De Roos et al. (15) the others distinguished between seropositive and seronegative RA cases.

Indicators of air pollution exposure also varied across studies. De Roos et al. (15) employed three different techniques. First, they used a geographic information system (GIS) to model proximity to the nearest highway or major road, where highways were defined as expressways or principal highways with average traffic counts of 114,000 and 21,000 motor vehicles per day; major roads were defined as secondary highways with average traffic counts of 15,000 and 18,000 vehicles per day. The authors used a land-use regression (LUR) model to calculate exposure to black carbon, NO, NO_2 and $PM_{2.5}$ as well as an inverse-distance weighting of the three air monitoring stations closest to the address to assess PM_{10}, O_3, SO_2 and NO_x. Hart et al. (16) also measured the proximity to the nearest primary and secondary roads, but they did not have data about traffic loads, instead relying only on Census feature class codes to classify them. Hart et al. (18) estimated NO_2, NO_x, SO_2, $PM_{2.5}$ and PM_{10} levels through dispersion modelling, but due to high correlations between some indicators, presented results only for NO_2, SO_2, and PM_{10}. Hart et al. (17) modeled NO_2, SO_2, $PM_{2.5}$, and PM_{10}.

Overall, all studies scored high on the NOS checklists (Table 2). De Roos et al. (15) received 8/9 stars because it was a nested case-control study and did not give response rates for both groups separately; in Hart et al. (16) the duration of exposure before diagnosis was not clearly stated. Regardless, all studies met the criteria for high quality. The following paragraphs provide a narrative description of study findings. See Table 3 for abstracted results for the main air pollution indicators.

3.3. Proximity to Road Traffic

Two studies used proximity to road traffic as a proxy for air pollution. De Roos et al. (15) conducted age- and sex-matched conditional logistic regression to study the odds

Table 1. Baseline Characteristics of Included Studies

Study	Design	Population	Rheumatoid Arthritis Assessment	Air Pollution Assessment	Duration of Exposure	Analysis	Adjustments
De Roos et al. (15)	Nested case-control (1999 - 2002)	Border air quality study, British Columbia; cases and controls (10 per case) selected from "at-risk" cohort members at the start of the 4-year follow-up (n = 640 041, 52.4% female); cases: RA-ICD-9 (n = 3 333), RA-prescription (n = 2 692) RA-specialist (n = 1 911)	ICD-9 (714.0 - 714.9); ICD-9 + RA-prescription; ICD-9 + RA-specialist; no distinction between types of RA	GIS-based proximity to nearest highways (21 000 vh/day) or major roads (18 000 vh/day): $\leq$ 50 m, 50 - 100 m, > 100 m; LUR models: black carbon, NO, NO_2, $PM_{2.5}$; inverse-distance weighting of monitoring stations: PM_{10}, O_3, CO, SO_2 (per IQR increase)	5 years before diagnosis	Conditional logistic regression (age- and sex-matched)	Age, sex and neighborhood SES
Hart et al. (17)	Cohort (1976 - 2006)	Nurses' health study, United States; (n = 11 425, 100% female, 55.9 years at follow-up)	Self-reported doctor-diagnosis + medical records (American college of rheumatology 1987 criteria); RA subtypes distinction	GIS-based: NO_2, SO_2, $PM_{2.5}$, PM_{10} (per IQR increase)	6, 10 years before diagnosis and time-varying cumulative average during follow-up	Time-varying Cox proportional hazards models	Age, race, smoking, menarche, parity, lactation, menopause, hormone use, contraceptives, physical activity, BMI, parents' occupation, education, marital status, husband's education, census-tract family income and house value
Hart et al. (18)	Case-control (1996 - 2008)	Epidemiological investigation of rheumatoid arthritis, Sweden; 51.5 (12.6) year at enrollment, $\approx$ 70% female, 1 497 cases/ 2536 controls	Rheumatologist examination, American College of Rheumatology 1987 criteria; RA subtypes distinction	Dispersion models: NO_2, SO_2, PM_{10} (per IQR increase)	5, 10, 20 years before diagnosis and average exposure	Conditional logistic regression (age- and sex-matched)	Age, sex, smoking, education
Hart et al. (16)	Cohort (1976 - 2004)	Nurses' health study, United States; (n = 90 297, 42.4 (7.1) years at baseline, 100% female)	Self-reported doctor-diagnosis + medical records (American college of rheumatology 1987 criteria); RA subtypes distinction	GIS-based proximity to nearest primary and secondary roads (US Census feature class code): $\leq$ 50 m, 50 - 200 m, > 200 m	Not reported explicitly	Time-varying Cox proportional hazards models	Age, race, smoking, menarche, parity, lactation, menopause, hormone use, contraceptives, physical activity, BMI, parents' occupation, education, marital status, husband's education, census-tract family income and house value

Abbreviations: BMI, body mass index; IQR, interquartile range; SES, socio-economic status; RA, rheumatoid arthritis.

Table 2. Quality Assessment of Included Studies (Newcastle-Ottawa Scale Items)

Studies		
Case-Control Studies		
	De Roos et al. (15)	**Hart et al. (18)**
Adequacy of case definition	*	*
Representativeness of the cases	*	*
Same source population for both groups	*	*
Definition of controls (no history of outcome)	*	*
Comparability (matched or adjusted for confounders - age + others)	**	**
Ascertainment of exposure (objective method)	*	*
Same method of exposure ascertainment for both groups	*	*
Same non-response rate in both groups	- (nested case-control)	*(96% vs. 83%)[a]
Overall score (9 max)	8	9
Cohort Studies		
	Hart et al. (16)	**Hart et al. (17)**
Representativeness of the exposed cohort	*	*
Same source population for the non-exposed cohort	*	*
Ascertainment of exposure (objective)	*	*
Demonstration that outcome of interest was not present at start of study	*	*
Comparability (matched or adjusted for confounders – age + others)	**	**
Assessment of outcome (objective and reliable)	*	*
Follow-up long enough for outcomes to occur[b]	Not reported explicitly	*
Adequacy of follow-up of cohorts	*	*
Overall score (9 max)	8	9

[a] Information obtained from another publication.
[b] Based on the premise that elevated autoantibodies were found 5 - 10 years prior to RA diagnosis (cited by Hart et al. (18)), 10 years was considered an acceptable exposure duration to observe some effect.

(OR) for RA in people living within 50 m of a road as opposed to those living > 150 m away. The models also were adjusted for neighborhood socioeconomic status. Living close to a highway or a major road was consistently associated with higher odds for RA. The highest OR (1.39, 95% CI: 1.16, 1.68) was observed for those living $\leq$ 50 m from a highway when RA was defined as $\geq$ 3 ICD-9 RA codes during follow-up (with two codes > 30 days apart); the models for the other two definitions did not differ considerably (OR of 1.37). As for proximity to a major road, the odds were elevated from 2% - 7% depending on the RA definition; however, they just fell short of statistical significance (OR = 1.07, 95% CI: 0.96, 1.19; OR = 1.07, 95% CI: 0.95, 1.20; and OR = 1.02, 95% CI: 0.92, 1.14, respectively). Sensitivity analyses showed that men living within 50 m of a highway had almost 60% higher odds (statistically significant) for RA, as opposed to women for whom the OR was just above 1.2 (non-significant).

Hart et al. (16) reported hazard ratios (HR) from Cox proportional hazards models for people living $\leq$ 50 m compared to those living > 200 m from a major road. The results were stratified based on participants' smoking status, subtype of RA and type of road involved. When A1-A3 roads (primary + secondary) were tested, the basic model (adjusted for age and calendar year) yielded a HR of 1.33 (95% CI: 1.00, 1.77). After additional adjustments for a wide range of potential covariates (Table 3), the HR retained its magnitude and became barely significant (1.31, 95% CI: 0.98 - 1.74). Among non-smokers, the effect was even higher and remained significant in the fully-adjusted model (HR = 1.62, 95% CI: 1.04, 2.52). If the type of RA was considered, participants had higher HRs for seropositive RA in the fully-adjusted model (HR = 1.44, 95% CI: 1.00, 2.07) than for seronegative RA, which noticeably fell short of statistical significance (HR = 1.15, 95% CI: 0.73, 1.83). Interestingly, the HR for seropositive RA rose among non-smokers; however, it also became non-significant, and the precision of the point estimate dropped (HR = 1.51, 95% CI: 0.82, 2.77). For seronegative RA and among non-smokers, the HR increased even more (HR = 1.77, 95% CI: 0.93, 3.38) compared to seropositive RA. Finally, considering only proximity to primary roads, the HR for those residing within 50 m was 1.63 (95% CI: 1.06, 2.51) in the whole cohort and 1.12 (95% CI: 0.46, 2.75) among non-smokers.

3.4. Particulate Matter

Two papers reported $PM_{2.5}$ effects, expressed as an increase in the effect size per one interquartile range (IQR) increase in $PM_{2.5}$. In the Border Air Quality Study, there were no elevated odds for RA in the fully-adjusted models (age, sex, and neighborhood socioeconomic status). Regardless of the definition of cases De Roos et al. (15) used, the ORs

Table 3. Abstracted Results for the Main Air Pollution Exposure Indicators

Exposure Indicator/Study	Metric in the Analysis	Risk for RA (Whole Sample)	Risk for RA (Stratified Analyses)	
			By Type of RA	By Smoking Status
Proximity to road traffic				
De Roos et al. (15)	$\leq$ 50 m vs. > 150 m	OR[a]	n/a	n/a
Hart et al. (16)	$\leq$ 50 m vs. > 200 m	HR[a]	ACPA+[a]	Non-smokers[b]
$PM_{2.5}$				
De Roos et al. (15)	Per 2.7 $\mu g/m^3$	OR	n/a	n/a
Hart et al. (17)	Per 5 $\mu g/m^3$	OR	ACPA[b]	None
PM_{10}				
De Roos et al. (15)	Per 0.87 $\mu g/m^3$	OR	n/a	n/a
Hart et al. (18)	Per 2 $\mu g/m^3$	OR[b]	ACPA-[b]	Smokers[b] (ACPA-)
Hart et al. (17)	Per 7 $\mu g/m^3$	HR	ACPA-[b]	None
NO_2				
De Roos et al. (15)	Per 6.3 $\mu g/m^3$	OR	n/a	n/a
Hart et al. (18)	Per 9 $\mu g/m^3$	OR[b]	ACPA-[a]	Smokers[a](ACPA-)
Hart et al. (17)	Per 15 $\mu g/m^3$	HR	ACPA+[b]	None
SO_2				
De Roos et al. (15)	Per 3.1 $\mu g/m^3$	OR	n/a	n/a
Hart et al. (18)	Per 8 $\mu g/m^3$	OR[a]	ACPA-[a]	Non-smokers[b]
Hart et al. (17)	Per 14 $\mu g/m^3$	HR	ACPA+[b]	Non-smokers[b]

Abbreviations: ACPA, anti-citrullinated peptide antibody; HR, hazard ratio; n/a, non-applicable; OR, odds ratio.
[a] Statistically significantly increased effect.
[b] Statistically non-significantly increased effect.

were consistently below 1.00. In the NHS, Hart et al. (17) also failed to observe elevated hazards for RA regardless of duration of exposure, adjustments, or smoking status. Interestingly, when the analyses were stratified by RA type, there were slightly elevated HRs (1%, non-significant) for seronegative RA in some adjusted models (those considering 6 years of exposure prior to diagnosis and the cumulative average exposure during follow-up).

With respect to PM_{10}, De Roos et al. (15) found no effect. Hart et al. (18) found marginally significant ORs of 1.01 (95% CI: 0.94, 1.09) and 1.02 (95% CI: 0.94, 1.10) in the base (age, sex) and fully-adjusted (age, sex, smoking status and educational attainment) models, respectively, only when they considered exposure 20 years prior to diagnosis. There were no effects noted for seropositive RA, whereas for seronegative RA, the odds ranged from 1% - 5% (marginally significant) depending on the duration of exposure considered. Further sensitivity analyses revealed that among smokers (especially for seronegative RA) and those with poorer education, the effects were generally more pronounced. As for Hart et al. (17) they observed elevated HRs of 1.02 (95% CI: 0.92, 1.14), 1.02 (95% CI: 0.92, 1.13), and 1.02 (95% CI: 0.91, 1.14) only for seronegative RA in the models with 6 and 10 years of exposure and cumulative average exposure during follow-up, respectively.

3.5. Nitrogen Dioxide and Sulfur Dioxide

Three papers reported results for NO_2. De Roos et al. (15) found no effect. When they used the RA-prescription definition, the ORs ranged from 0.89 (95% CI: 0.84, 0.94) to 0.95 (95% CI: 0.90, 0.99) with the RA-ICD-9 definition. Hart et al. (18) on the other hand, found marginally significant odds for RA across all duration of exposure scenarios, ranging from 1.02 (95% CI: 0.95, 1.09) (exposure 20 years before diagnosis) to 1.09 (95% CI: 0.99, 1.19) (exposure 10 years before diagnosis) in the fully-adjusted models. The ORs for seronegative RA were statistically significant in the fully-adjusted models considering exposure 5 years (OR = 1.19, 95% CI: 1.01, 1.40) and 10 years (OR = 1.22, 95% CI: 1.07, 1.40) before diagnosis. The effects were stronger among poorly-educated participants (either statistically significant or marginally significant for seronegative RA). Among

smokers, the odds were generally higher only when considering exposure levels 5 years before diagnosis, and they were statistically significant only for seronegative RA. In the NHS, (17) the only elevated HR was for seropositive RA when the authors considered the cumulative average exposure during follow-up – 1.03 (95% CI: 0.91, 1.16) in the fully-adjusted model.

The same three studies measured SO_2 levels. De Roos et al. (15) showed no effect per 3.1 $\mu g/m^3$ (ORs < 1.00). Hart et al. (18) reported elevated ORs across the models regardless of duration of exposure. In the base models (adjusted for age and sex), the ORs were significant – 1.28 (95% CI: 1.06, 1.55) and 1.12 (95% CI: 1.05, 1.21) for 10 and 20 years of exposure, respectively; the fully-adjusted model (20 years of exposure) was marginally significant (OR = 1.08, 95% CI: 1.00, 1.16). Among those with no university education, the odds were higher (especially for seronegative RA). As for smoking status, non-smokers had higher ORs that became statistically significant in the 10 years prior to the diagnosis exposure scenario. According to RA type, the effects for seronegative RA were more pronounced and statistically significant in the fully-adjusted models considering exposure levels 10 and 20 years before diagnosis OR = 1.48 (95% CI: 1.13, 1.95) and OR = 1.14 (95% CI: 1.03, 1.26), respectively. Hart et al. (17) did not find elevated HRs in the whole sample and reported only non-significant effects for seropositive RA and among non-smokers.

3.6. Other Exposures (Nitrogen Oxide, Ozone, Black Carbon and Carbon Monoxide)

Only De Roos et al. (15) studied other indicators of air pollution. NO was not associated with any effect. Interestingly, they reported higher odds per 8.4 $\mu g/m^3$ increase in O_3 ranging from OR = 1.07 (95% CI: 0.98, 1.16) to OR = 1.26 (95% CI: 1.18, 1.36) for RA-specialist and RA-prescription diagnosis, respectively. These effects were considerably stronger in people < 65 years of age. Black carbon and CO were not risk factors for RA.

4. Conclusions

4.1. Summary of Evidence

Four relevant papers comprising three datasets were included in the qualitative synthesis. The two studies reporting results for proximity to road traffic showed consistently higher and statistically significant risks for RA in people living within 50 m of a heavy traffic road. In Hart et al. (16) the effects were stronger for seropositive RA and among non-smokers. No firm conclusions could be made for particulate matter. Based on two studies, $PM_{2.5}$ was not associated with higher odds for RA in the main analyses. For PM_{10}, only Hart et al. (18) reported elevated OR, which failed to reach statistical significance. The effects of both $PM_{2.5}$ and PM_{10} were non-significant across the analyses but consistently more pronounced for seronegative RA. Only one study found NO_2 to be associated with statistically significant odds for seronegative RA and among smokers. The risks for both types of RA and for seronegative RA per one IQR increase in SO_2 were significant in one out of three relevant studies. In the only study for O_3, De Roos et al. (15) found significantly higher odds for RA.

Overall, proximity to road traffic appears to be an important risk factor for RA. As for particular pollutants, only Hart et al. (18) provided evidence of elevated risks for NO_2 and SO_2, especially in terms of seronegative RA. Possible reasons for the non-elevated risks reported by others might be the short duration of exposure considered by De Roos et al. (15) or their study's small variability in air pollution levels compared to Hart et al. (18). The effects of particulate matter were higher for seronegative RA, while findings were discordant regarding the effects of NO_2 and SO_2 on the subtypes of RA. Also inconsistent were the associations between smoking and the effects of air pollution.

4.2. Limitations and Future Research

Despite our rigorous literature search, only four papers relevant to the research question were retrieved with no more than three distinct datasets per any particular contaminant. This fact precludes us from making strong inferences about the effects of air pollution on RA, rendering virtually all evidence preliminary and inconclusive. However, the low number of included primary studies should be viewed as a limitation in the research field. The merit of a systematic review should not be judged by the available body of evidence but by the possibility of omitted evidence which was not the case here. In fact, when no eligible studies are identified, "empty reviews" are created, numbering up to 9% of those in the Cochrane database of systematic reviews (19). As a result of effect size estimates per contaminant, we did not conduct a quantitative meta-analysis. Such analysis was further hindered by the different effect sizes reported in the studies. Although HRs and ORs are often treated as relative risk estimates in practice, they are epidemiologically and statistically different from the relative risk and from each other (20, 21). Based on the reviewed literature, the risk for RA could not be linked to particular contaminant concentrations, and no threshold effects or exposure-response functions could be discerned.

The significant effects associated with proximity to road traffic might be explained by the fact that this measure is closer to the epidemiological reality by including information regarding traffic exhaust, psychological reactions to the traffic itself, and noise exposure. At this forma-

tive stage, this measure is easy to use because we are more interested in whether there are elevated risks for people exposed to traffic emissions rather than generating precise exposure-response relationships. With respect to individual contaminants, the studies should ensure sufficient variability in exposure data in order to detect effects. Adjustments are essential for residential noise and occupational exposure to noise and air pollutants as well as for the type of domestic heating. The interactions between smoking status, air pollution and RA type are of particular interest. Researchers should report analyses and effect size estimates comparable with previous studies in order to facilitate quantitative meta-analyses.

An alternative explanatory framework merits further investigation. Given that air pollution levels have been higher internationally in the past (22-24), we are left pondering why the alleged association between air pollution and RA is just starting to emerge. One reason might be that geographic information systems were introduced in environmental epidemiology research relatively recently and that the quality of air pollution modelling has improved, thus providing us the opportunity to uncover these associations. The difference in study designs should also be kept in mind; exposure-outcome relationships on the individual level might not be observed in an ecological study and vice versa. In addition to these methodological considerations, to further reinforce the biological grounds for epidemiological research, we should consider the effects of nutritional habits and air pollution contamination during pregnancy, which affects connective tissue development (intrauterine programming) (25). Finally, some residual socio-demographic and cartographic confounding cannot be ruled out; therefore, the causal link between air pollution and RA might need to be revisited.

Based on two high quality studies, proximity to road traffic might be considered a risk factor for RA. Although the results for NO_2 and SO_2 are discordant, there are suspected effects associated with those contaminants as well. Overall, the available evidence is too preliminary and scarce to draw firm conclusions; however, the results indicate the feasibility of further studies elucidating on the relationship between air pollution and RA.

Footnote

Authors' Contribution: Angel Mario Dzhambov developed the review idea, conducted literature searches, interpreted the results, and drafted the manuscript. Donka Dimitrova Dimitrova conducted literature searches, developed the review protocol, supervised, and critically revised the manuscript. Tanya Hristova Turnovska conducted literature searches and critically revised the manuscript.

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