TABLE 1 Baseline characteristics of personal case series and RAPS study

Characteristics	Personal case series (*n* = 4)	RAPS study (*n* = 57)
Age, mean (S.D.), years	34.5 (16.4)	47 (17)
Gender, *n*/*N* (%)		
Women	2/4 (50)	42/57 (74)
Male	2/4 (50)	15/57 (26)
Number of criteria for definite APS, mean (S.D.)	1.5 (1)	NR
History of clinical manifestations, *n*/*N* (%)		
Venous thrombosis	4/4 (100)	57/57 (100)
Arterial thrombosis	1/4 (25)	0/57 (0)
Small vessel thrombosis	1/4 (25)	NR
Obstetrical morbidity	0/4 (0)	NR
aPL profile, *n*/*N* (%)		
Double positivity	0/4 (0)	16/57 (28)
Triple positivity[a]	4/4 (100)	7/57 (12)
Underlying autoimmune disease, *n*/*N* (%)		
Primary APS	2/4 (50)	NR
Associated APS	2/4 (50)	NR
SLE	2/4 (50)	11/57 (19)

[a]Triple positivity: LA and aCL antibodies and anti-β_2-GPI antibodies. *N*: total number of patients in the study; *n*: patients fulfilling the characteristic; NR: not reported.

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Virginie Dufrost[1], Jessie Risse[1,2], Stéphane Kirchner[3], Stéphane Zuily[1,2] and Denis Wahl[1,2]

[1]*CHRU de Nancy, Vascular Medicine Division and Regional Competence Center for Rare Vascular and Systemic Autoimmune Diseases,* [2]*Inserm UMR_S 1116 School of Medicine, Lorraine University and* [3]*Department of Pathology, Pathology Center Emile Gallé, Nancy, France*
Revised version accepted 1 March 2017
Correspondence to: Denis Wahl, CHRU de Nancy, Service de Médecine Vasculaire et Centre de Compétence Régional des Maladies Rares Vasculaires, Systémiques et Auto-Immunes, Institut Lorrain du cœur et des vaisseaux Louis-Mathieu, rue du Morvan, 54511 Vandoeuvre-Lès-Nancy Cedex, France.
E-mail: d.wahl@chru-nancy.fr

References

1 Miyakis S, Lockshin MD, Atsumi T *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.

2 EINSTEIN Investigators, Bauersachs R, Berkowitz SD *et al*. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499–510.

3 Son M, Wypasek E, Celinska-Lowenhoff M, Undas A. The use of rivaroxaban in patients with antiphospholipid syndrome: a series of 12 cases. Thromb Res 2015;135:1035–6.

4 Betancur JF, Bonilla-Abadía F, Hormaza AA *et al*. Direct oral anticoagulants in antiphospholipid syndrome: a real life case series. Lupus 2016;25:658–62.

5 Pengo V, Ruffatti A, Legnani C *et al*. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood 2011;118:4714–8.

6 Cohen H, Hunt BJ, Efthymiou M *et al*. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. Lancet Haematol 2016;3:e426–36.

7 Dufrost V, Risse J, Zuily S, Wahl D. Direct oral anticoagulants use in antiphospholipid syndrome: are these drugs an effective and safe alternative to warfarin? A systematic review of the literature. Curr Rheumatol Rep 2016;18:74.

8 Pengo V, Banzato A, Bison E *et al*. Efficacy and safety of rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome: Rationale and design of the Trial on Rivaroxaban in AntiPhospholipid Syndrome (TRAPS) trial. Lupus 2016;25:301–6.

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Comment on: Increased inflammation and disease activity among current cigarette smokers with rheumatoid arthritis: a cross-sectional analysis of US veterans

SIR, I read the study by Sokolove and colleagues [1] with interest. The authors demonstrated both increased disease activity measured by Disease Activity Score 28

joints (DAS28) and increased levels of a panel of pro-inflammatory cytokines and chemokines by a multiplex method, in current smokers compared with never or former smoking veterans with RA. Importantly, a panel of 30 citrullinated proteins (ACPA) associated neither with the cytokine and chemokine panel nor with the DAS28 in current smokers.

They ascribe the higher DAS28 and cytokine panel solely to the effects of smoking, which, indeed, has been shown to increase the production of ACPA in response to periodontal and lung disease. From a review of the references in the Sokolove study, smoking is likely to be associated with more severe RA disease activity and ultimate structural damage seems likely. This literature, however, is not consistent. Other studies have failed to document structural damage. This was also true of the Sokolove study [1]. Although the authors did include the co-morbidity count in their calculations, analysis of depression and FM prevalence was not done, and this is a problem.

The renowned philosopher of science Karl Popper wrote, 'Every genuine test of a theory is an attempt to falsify it, or refute it'. The purpose of this letter is to refute the implicit hypothesis that smoking alone was the sole mechanism responsible for the findings. Other unmeasured factors with mechanisms of their own are at play.

The DAS28 may be modified by a number of mechanisms. In the general public, smoking is associated with increased painful musculoskeletal conditions compared with non-smokers, as well as a higher prevalence of depression [2, 3]. Associated painful musculoskeletal conditions might well disproportionately increase patient global assessment and tender joint count. Co-morbid depression in RA, estimated to be as high as 38%, is also associated with disproportionate elevation of the tender joint count and patient global assessment, subjective components of DAS model indices [4]. Lastly, the prevalence of fibromyalgia syndrome (FMS) in RA, estimated to be ~20%, is also associated with this same disproportionate elevation of subjective components of the DAS28. Furthermore, the prevalence of smoking is higher in individuals with FMS than in the general population and FMS smokers have more severe FMS symptoms. The physiological mechanism for this phenomenon is based on deregulation of balance between leptin and neuropeptide Y [5].

The relationships among these observations are obvious, and suggest an alternative hypothesis: that RA current smokers have more depression and a higher prevalence of more severe FMS. These factors increase the smoker DAS28 by inflating subjective components. The absolute magnitude of the DAS28, thought to be due solely to inflammation as a direct effect of smoking on biological RA disease activity, after subtraction of the independent effects of smoking, depression and FMS, would be lower than what is here reported.

A TNFi treatment study is consistent with this hypothesis. When the individual components of DAS28 were examined, the authors found lower response of the subjective components compared with objective components in ever smokers [6]. The authors postulated greater sensitivity to non-inflammatory pain in ever smokers compared with never smokers to explain these findings. Unfortunately, they did not include depression or FM in their analysis.

There is some evidence that these mechanisms are at play in the Sokolove study. The magnitude of the ESR did not associate with the high DAS28 of current smokers. Although the CRP was slightly elevated and associated with current smokers, its level of statistical significance was lost after multivariable analysis. These two very objective measures of disease activity were not increased in smokers despite clinical measure elevations.

As for cytokine elevation, both depression and smoking elevate inflammatory cytokines such as IL-6 in the general population. Although these elevations are relatively small, they are still statistically significant. Higher cytokines, primarily from depression and smoking, through their own independent mechanisms, provide an additive effect, which would produce a higher, inflated value for cytokines, not entirely reflecting biological RA disease activity.

This study illustrates potential problems that occur when measures of depression such as the Patient Health Questionnaire-9 and Polysymptomatic Distress score for FMS are not incorporated into DAS index model studies. These instruments in common use to estimate RA disease activity are influenced not only by RA biological disease activity, but also by psychological state and relative distress. These two factors must be measured in order to understand their relative contribution to the final score.

The preceding analysis also applies to the Modified Health Assessment Questionnaire. As in this study, it has often been found higher in smokers compared with never smokers. The various Health Assessment models have been shown to be similarly modified and inflated by co-morbid depression and FMS [7].

This analysis has ramifications beyond application to the Sokolove study. Failure to recognize depression and other factors that inappropriately inflate the DAS28 has led to treatment that was more aggressive than necessary, and potentially more dangerous [8].

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William S. Wilke[1]

[1]*Private residence, Cleveland, OH, USA*
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Correspondence to: C/O Rheumatology Editorial Office, Bride House, 18–20 Bride Lane, London EC4Y 8EE, UK.
E-mail: wswilkemd@gmail.com

References

1 Sokolove J, Wagner CA, Lahey LJ *et al*. Increased inflammation and disease activity among current cigarette smokers with rheumatoid arthritis: a cross-sectional analysis of US veterans. Rheumatology 2016;55:1969–77.

2 Palmer KT, Syddall H, Cooper C, Coggen D. Smoking and musculoskeletal disorders: findings from a British national survey. Ann Rheum Dis 2003;62:33–6.

3 Centers for Disease Control and Prevention (CDC). Vital signs: current cigarette smoking among adults aged ⩾18 years with mental illness – United States, 2009-2011. MMWR Morb Mortal Wkly Rep 2013;62:81–7.

4 Matcham F, Ali S, Irving K *et al*. Are depression and anxiety associated with disease activity in rheumatoid arthritis? A prospective study. BMC Musculoskel Disord 2016;17:155.

5 Bokarewa MI, Erlandsson MC, Bjersing J *et al*. Smoking is associated with reduced leptin and neuropeptide Y levels and higher pain experience in patients with fibromyalgia. Mediators Inflamm 2014;2014:627041.

6 Mattey DL, Brownfield A, Dawes PT. Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. J Rheumatol 2009;36:1180–7.

7 Michaud K, Wallenstein G, Wolfe F. Treatment and nontreatment predictors of health assessment questionnaire disability progression in rheumatoid arthritis: a longitudinal study of 18,485 patients. Arthritis Care Res 2011;63:366–72.

8 Lage-Hansen PR, Chrysidis S, Lage-Hansen M *et al*. Concomitant fibromyalgia in rheumatoid arthritis is associated with the more frequent use of biological therapy: a cross-sectional study. Scand Rheumatol 2016;45:45–48.

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Comment on: Increased inflammation and disease activity among current cigarette smokers with rheumatoid arthritis: a cross-sectional analysis of US veterans: reply

Sir, We were pleased to read the letter by Dr Wilke in response to our recent article addressing the association of smoking with disease activity in RA [1]. Dr Wilke points out that depression and anxiety are associated with worse patient-related outcomes in RA. Indeed, our group has previously published, for the same cohort, the association of depression and/or anxiety with disease activity measures in RA, demonstrating robust associations with more patient-reported measures such as pain, tender joint counts, Multidimensional Health Assessment Questionnaire score and patient global assessment, and less striking associations with DAS-28 [2]. Using the same diagnostic codes that were used in this prior effort, we have now examined the associations of smoking with both DAS28 and cytokine score after accounting for confounding due to depression and/or anxiety. We found that the associations of current smoking (referent to former or never smoking) with DAS-28 and cytokine score were not changed following adjustment for depression and/or anxiety.

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Jeremy Sokolove[1,2], Harlan Sayles[3,4] and Ted Mikuls[3,4]

[1]*Veterans Affairs Palo Alto Health Care,* [2]*Department of Medicine, Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA,* [3]*Veterans Affairs Nebraska Western-Iowa Health Care System and* [4]*Nebraska Arthritis Outcomes Research Center, University of Nebraska Medical Center, Omaha, NE, USA*
Accepted 14 March 2017
Correspondence to: Jeremy Sokolove, Veterans Affairs Palo Alto Health Care System, Mail Stop 111G, 3801 Miranda Avenue, Palo Alto, CA 94304, USA.
E-mail: sokolove@stanford.edu

References

1 Wilke WS. Comment on: Increased inflammation and disease activity among current cigarette smokers with rheumatoid arthritis: a cross-sectional analysis of US veterans. Rheumatology 2017;56:1434–6.

2 Mikuls TR, Padala PR, Sayles HR *et al*. Prospective study of posttraumatic stress disorder and disease activity outcomes in US veterans with rheumatoid arthritis. Arthritis Care Res 2013;65:227–34.

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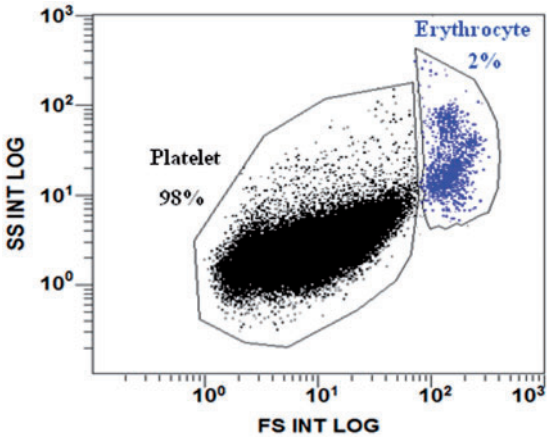
Comment on: Decreased platelet size is associated with platelet activation and anti-phospholipid syndrome in systemic lupus erythematosus

We read the article written by Lood *et al.* [1] with great interest. In this article we noticed that Fig. 1A shows the flow cytometry analysis of isolated platelets. Specifically,

Fig. 1 Representative platelet gating criteria for platelet detection



In this gating strategy, the discrimination value was set to zero; platelets (98%) and erythrocytes (2%) are displayed.