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Association of high body lead store with severe intracranial carotid atherosclerosis

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ABSTRACT

Objective: Lead is involved in the pathogenesis of atherosclerosis and hypertensive disease and may be related to cerebrovascular disease. We studied the association of body lead level with stroke subtypes and severity of cerebral atherosclerosis in order to identify the significance of lead exposure to cerebrovascular disease.

Methods: From April, 2002 to March, 2005, we studied the lead level in all patients receiving digital subtraction angiography. Diameter stenosis at extracranial carotid, intracranial carotid and vertebrobasilar system was calculated according to the NASCET criteria. A blood sample and a mobilization test of 72-h urine sample were collected for lead measurement.

Results: In a total of 213 subjects, 19 were free of stroke (blood lead level = 4.62 ± 2.41 μg/dL, body lead store = 39.04 ± 20.91 μg) and 194 were stroke patients (4.89 ± 2.75 μg/dL, 45.13 ± 29.8 μg; all stroke vs. non-stroke, $P > 0.05$). In the 153 subjects with atherosclerotic origin, body lead store but not blood lead level in the intracranial carotid system was significantly higher in ≥50% group than <50% group (blood lead: 5.61 ± 3.02 μg/dL vs. 4.80 ± 2.50 μg/dL, Student's *t*-test, $P = 0.129$; body lead store: 51.7 ± 27.0 μg vs. 41.9 ± 23.5 μg, Student's *t*-test, $P = 0.038$, multivariate logistic regression, odds ratio = 1.02, 95% CI: 1.00–1.03, $P = 0.043$). However, there was no significant association between lead level and stenotic severity in extracranial and vertebrobasilar systems ($P > 0.05$).

Conclusion: Our study demonstrated that long-term lead exposure as measured by body lead store might carry a potential risk of intracranial carotid atherosclerosis.

1. Introduction

Previous studies indicated that lead has specific toxicities in the proliferation, fibrinolysis, and extracellular matrix formation of vascular endothelial and smooth muscle cells, resulting in vascular disorders such as atherosclerosis in experimental animals (Kaji, 2004). Lead may induce aortic atherosclerosis in pigeons (Revis et al., 1981) and stimulate the proliferation of cultured rabbit aortic smooth muscle cells in varying degrees (Lu et al., 1990). Lead can also stimulate the proliferation of the vascular smooth muscle cells and fibroblasts (Fujiwara et al., 1995) and inhibit the repair process of damaged endothelial cell layer (Fujiwara et al., 1997) in in vitro studies. Animal study showed that lead may cause severe injury to endothelium of brain vasculature (Bradbury and Deane, 1988; Linnamagi and Kaasik, 1995) and induces cerebral microvascular dysfunction with following changes in cerebral blood flow (Linnamagi and Kaasik, 1995). Hence, it is likely that lead is involved in the pathogenesis of cerebral atherosclerosis and may be related to cerebrovascular disease.

Cerebrovascular disease or stroke has been one of the first three leading causes of death in the past four decades in Taiwan (Jeng and Su, 2007) and is more common in Taiwanese than in Whites (Hu et al., 1992; Goldstein et al., 2006). The distribution of cerebral atherosclerosis in stroke patients is different between races, and atherosclerosis of the larger extracranial arteries is more prevalent in Whites, while occlusive disease of the intracranial arteries is more often seen in patients of Black or oriental origin (Feldmann et al., 1990; Leung et al., 1993; Liu et al., 1996; Jeng and Su, 2007). Regarding stroke subtype, small vessel occlusion and large artery atherosclerosis are related to atherosclerosis, while strokes of cardiogenic embolism and other determined etiology are less related. Hemorrhagic stroke is more common in oriental people

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Article Structure

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intracranial and extracranial atherosclerosis with high accuracy. However, due to the invasiveness and ethical concern, the angiographic study is unable to apply in every stroke patient, and it is likely that we studied a group of patients with high risk of atherosclerosis. Third, we examined both single blood lead level and 72-h urine lead amount to calculate body lead store for this study. The body lead store can represent the chronic exposure to lead and is able to examine the long-term influence of lead on atherosclerosis. Our study suggests that body lead store might be more sensitive than single blood lead level in the prediction of atherosclerosis.

In conclusion, our study showed that long-term exposure to lead might carry a potential risk of intracranial carotid atherosclerosis.

Conflict of interest

Authors have nothing to declare.

Acknowledgments

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2. Materials and methods

2.1. Patient enrollment

From April, 2002 to March, 2005, we conducted this cross-sectional study in all patients receiving cerebral digital subtraction angiography in the Department of Neurology, Chang Gung Memorial Hospital, Linkou Medical Center. All patients received chest X-ray, electrocardiogram, complete blood count (hemoglobin, hematocrit, platelet, leucocyte), blood glucose, electrolytes, or TIA were classified into non-atherosclerosis group, if the vascular lesion was due to etiologies other than atherosclerosis, such as vascular anomaly and vasculopathy due to radiation.

2.4. Measurement of lead

In the present study, we examined the single blood lead level and total 72-h urine lead amount (body lead store) before cerebral angiography. Body lead store was determined according to our previous method (Lin et al., 2003) which used the mobilization test developed by Emmerson (1963) and modified by Behringer et al. (1986). Each subject emptied his or her bladder on the first day of

3. Results

During the study period, a total of 221 patients received cerebral angiography. Of them, 116 patients had extracranial carotid stenosis (≥50% diameter stenosis), 63 had intracranial carotid stenosis, 97 had vertebrobasilar stenosis, and 64 had <50% stenosis in all vascular territory. Three subjects had blood lead level and body lead store exceeding three standard deviations of the corresponding measure, and five subjects did not receive complete blood and urine lead collection; these eight subjects were excluded from analysis. Among the rest 213 subjects and body lead store when compared to other determined etiology (Student's *t*-test, $P = 0.001$ and 0.043, respectively), but there was no significance in multivariate logistic regression analysis ($P > 0.05$). Hemorrhagic stroke had significantly lower blood lead level than large artery atherosclerosis in univariate analysis (Student's *t*-test, $P = 0.009$), but not in multivariate analysis after adjustment for age, sex, HT, DM, cholesterol, triglyceride, uric acid, smoking and alcohol consumption ($P > 0.05$).

To study the association between atherosclerotic severity and lead level, the eight subjects with hemorrhagic stroke were excluded from analysis. Table 2 shows that in the 205 subjects, 52

4. Discussion

Previous autopsy study reported a positive association between tissue lead level and risk of heart-related mortality (Voors et al., 1982). Some cohort studies found a positive association of blood lead level due to environmental exposures with the risk of cardiovascular and stroke mortality (Menke et al., 2006; Schober et al., 2006), with the prevalence of peripheral artery disease

Several strengths and limitations of this study should be considered. First, our analysis showed that among different stroke subtypes, large artery atherosclerosis tends to have higher blood lead level and body lead store, though with no statistical significance. The statistical insignificance might be due to a small sample size. Second, we used the gold standard of digital subtraction angiography to examine cerebral vasculature. The detailed cerebral artery study can make a clear classification of TOAST stroke subtypes and allow us to evaluate the severity of

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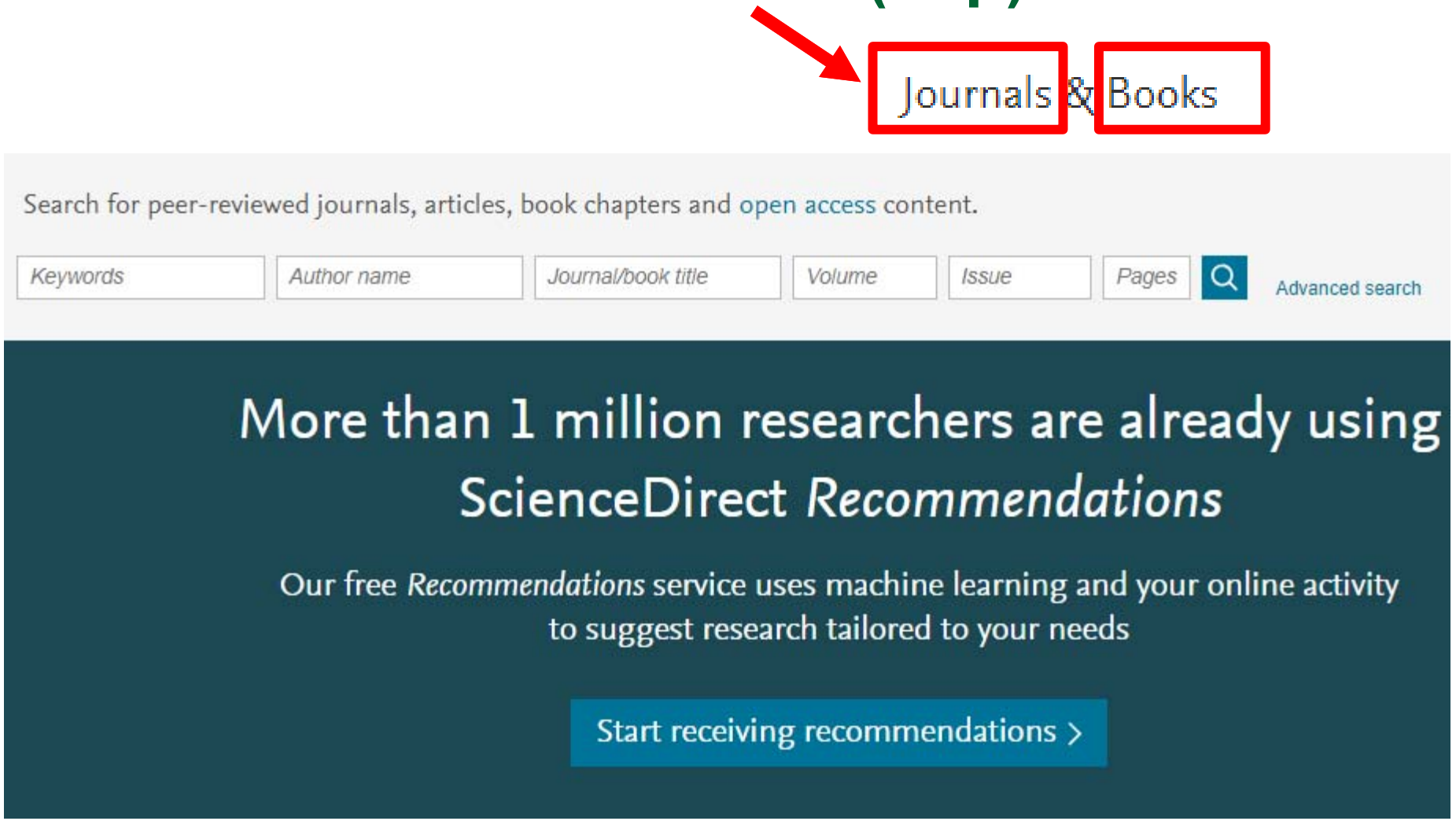

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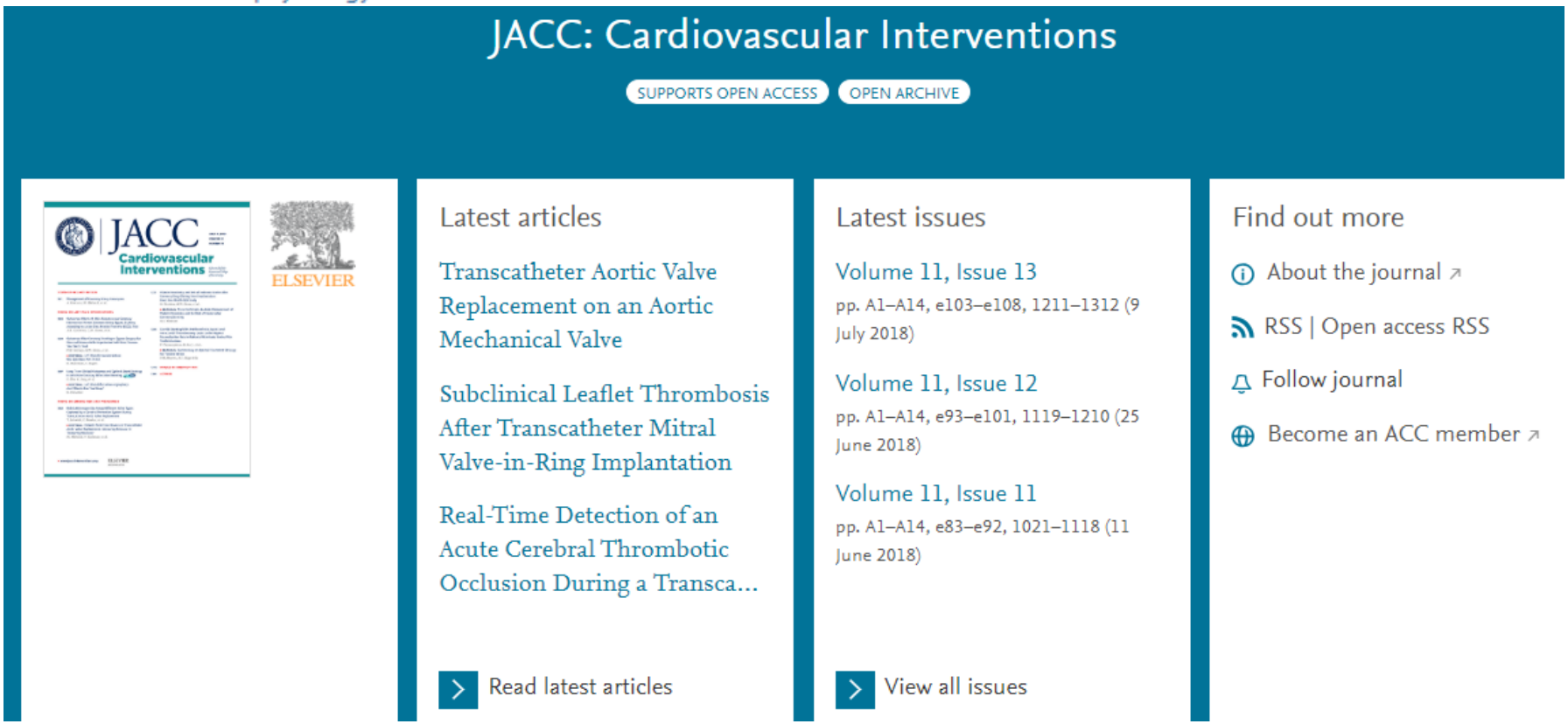

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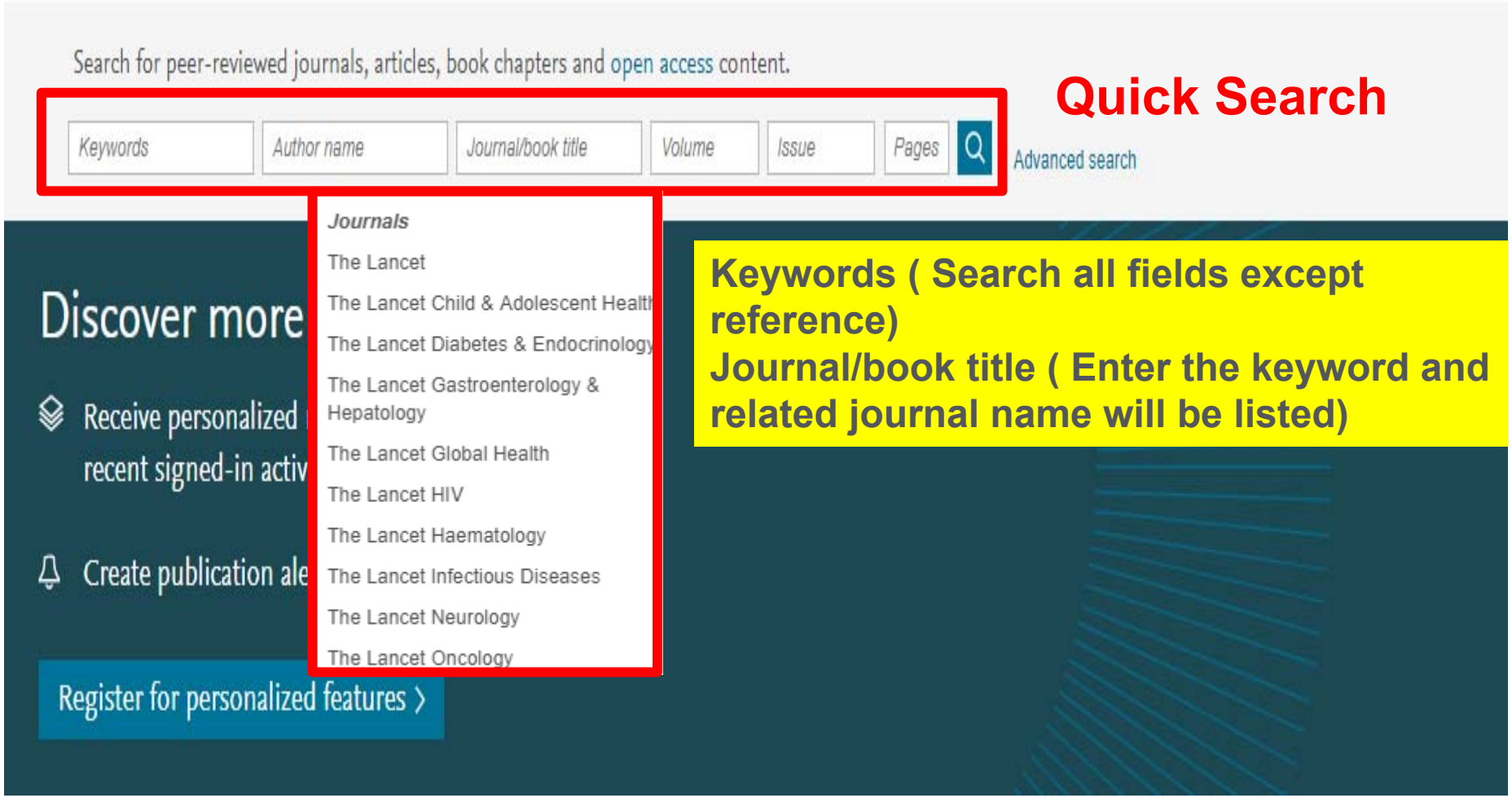

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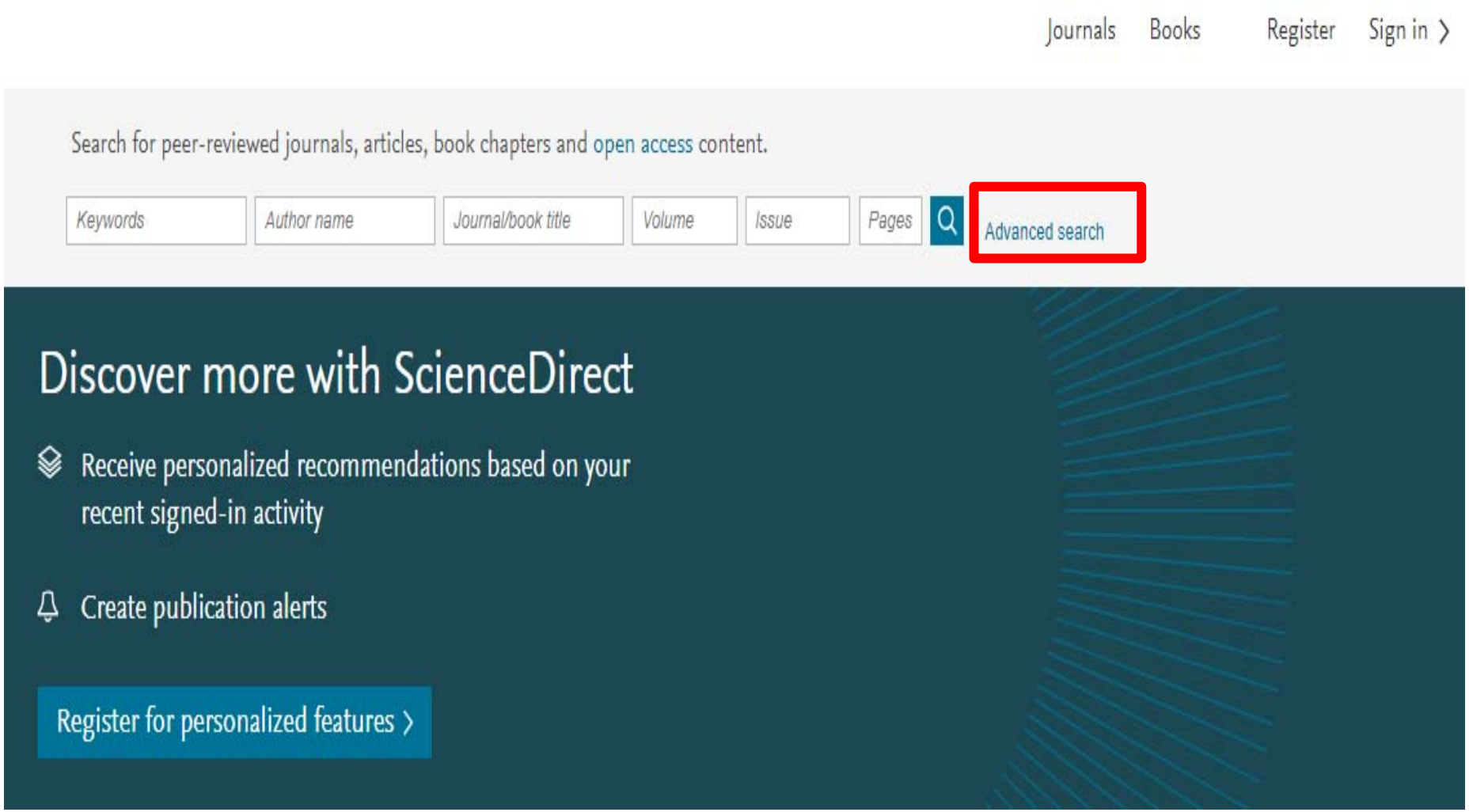

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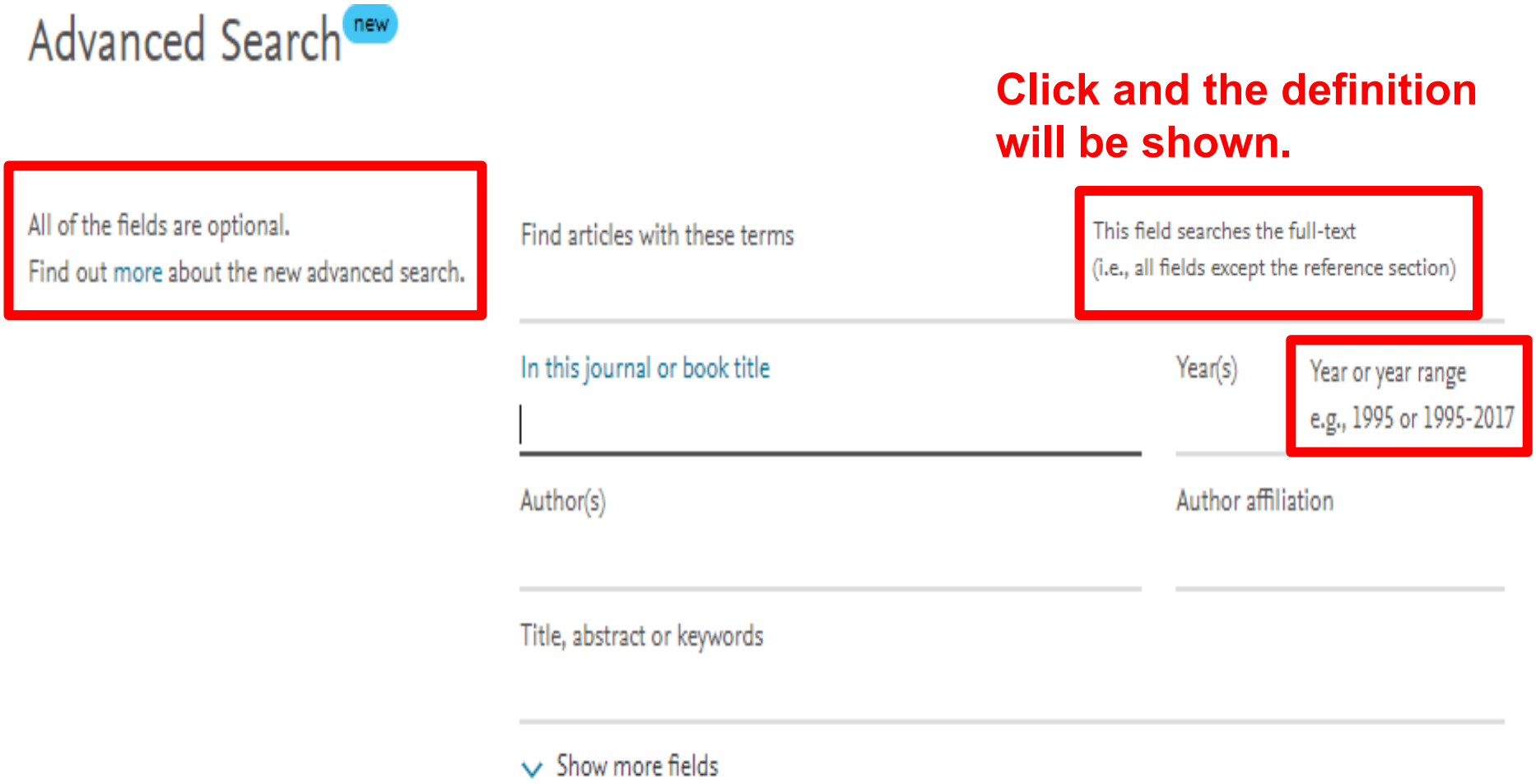

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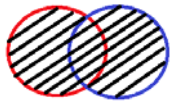
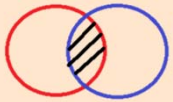
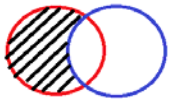
	**OR**	At least 1 keyword is shown，e.g. liver OR cirrhosis. Sometimes for synonyms.
	**AND**	The two keywords need to be shown, e.g. "Cognitive architecture" AND robots
	**NOT**	Exclude keywords，e.g. lung NOT cancer or lung -cancer

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“”	Quotation mark can be used to specify terms which must appear next to each other e.g. type “heart attack”，the result will include heart attack、heart-attack、heart attacks.

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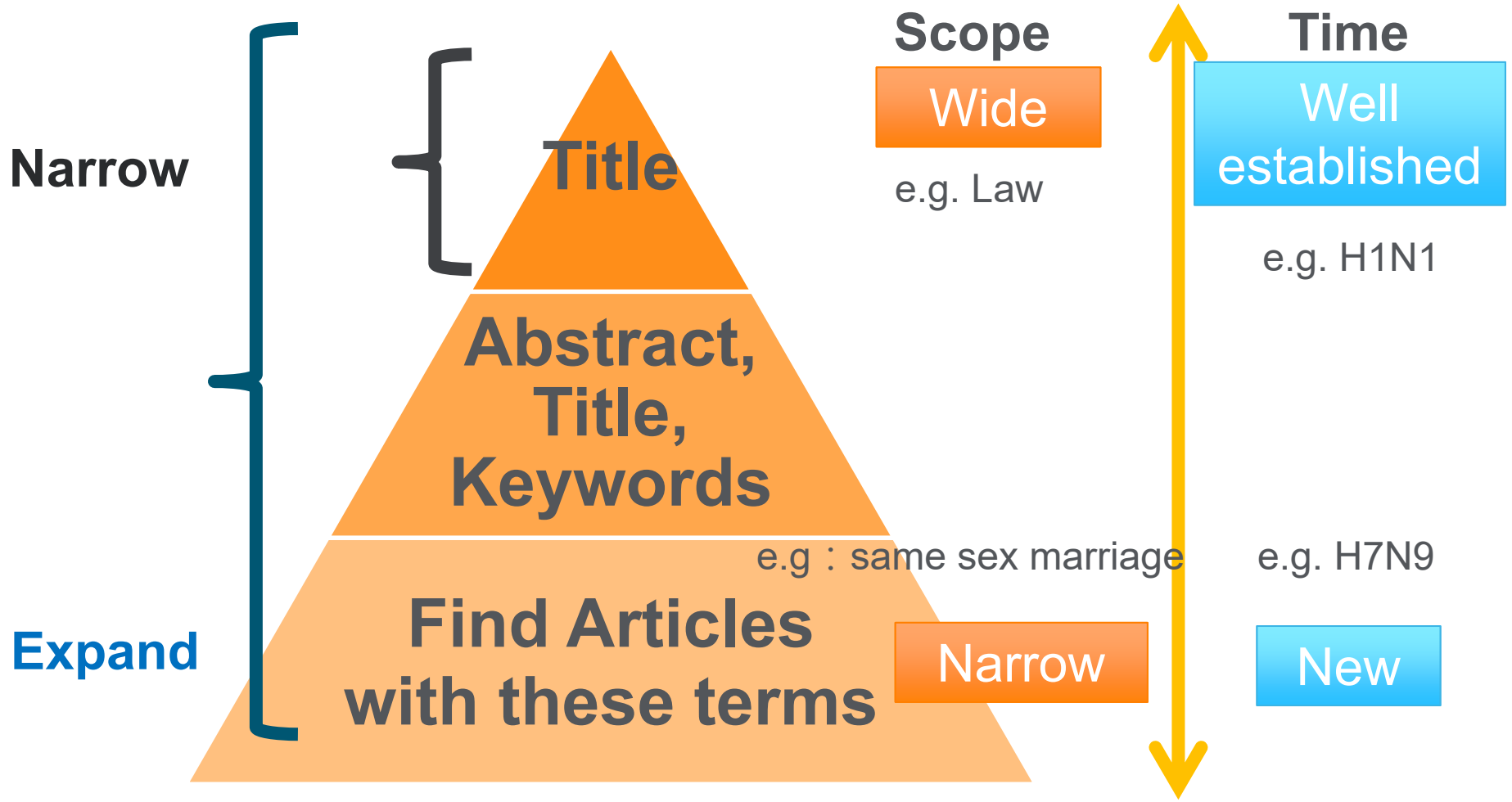

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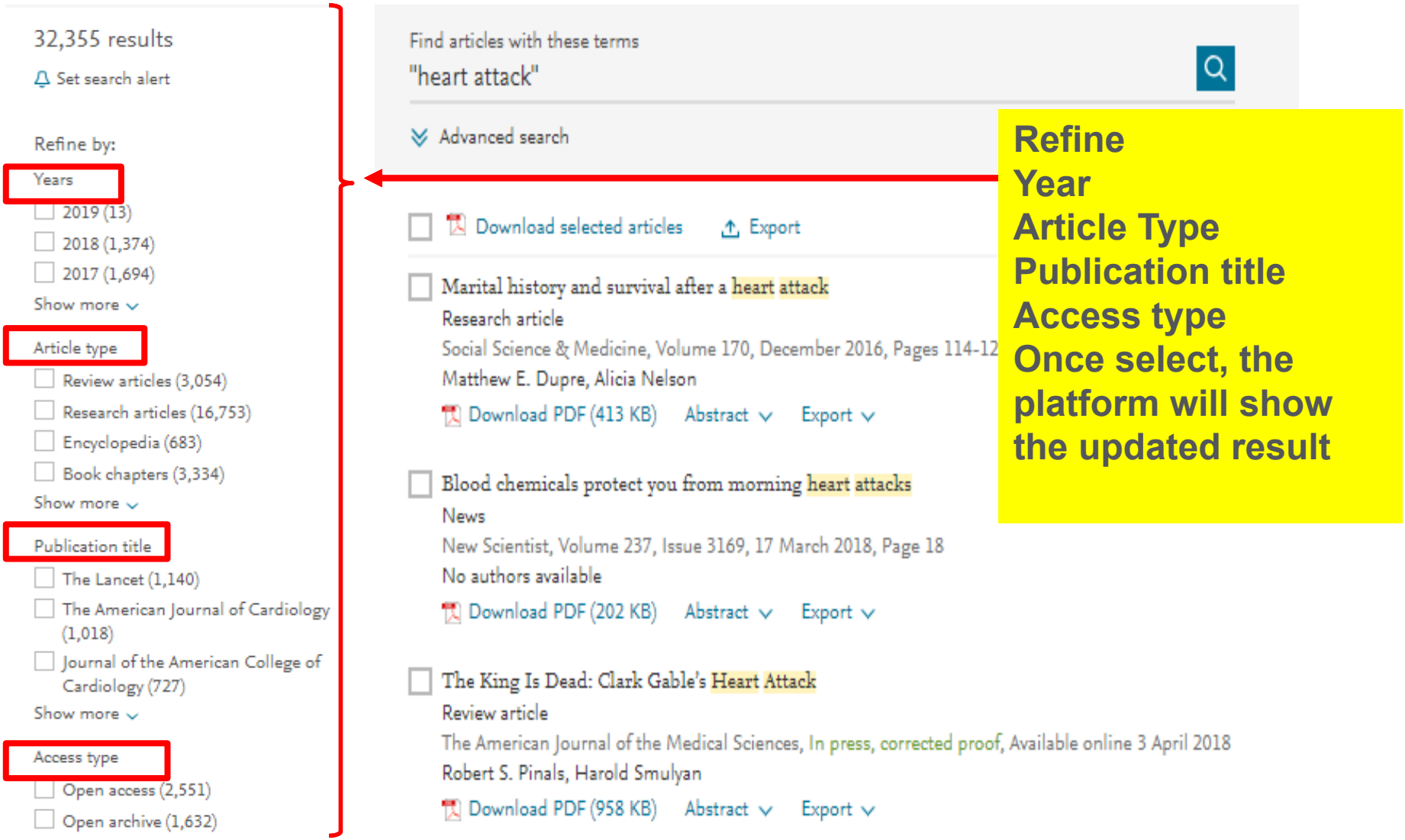

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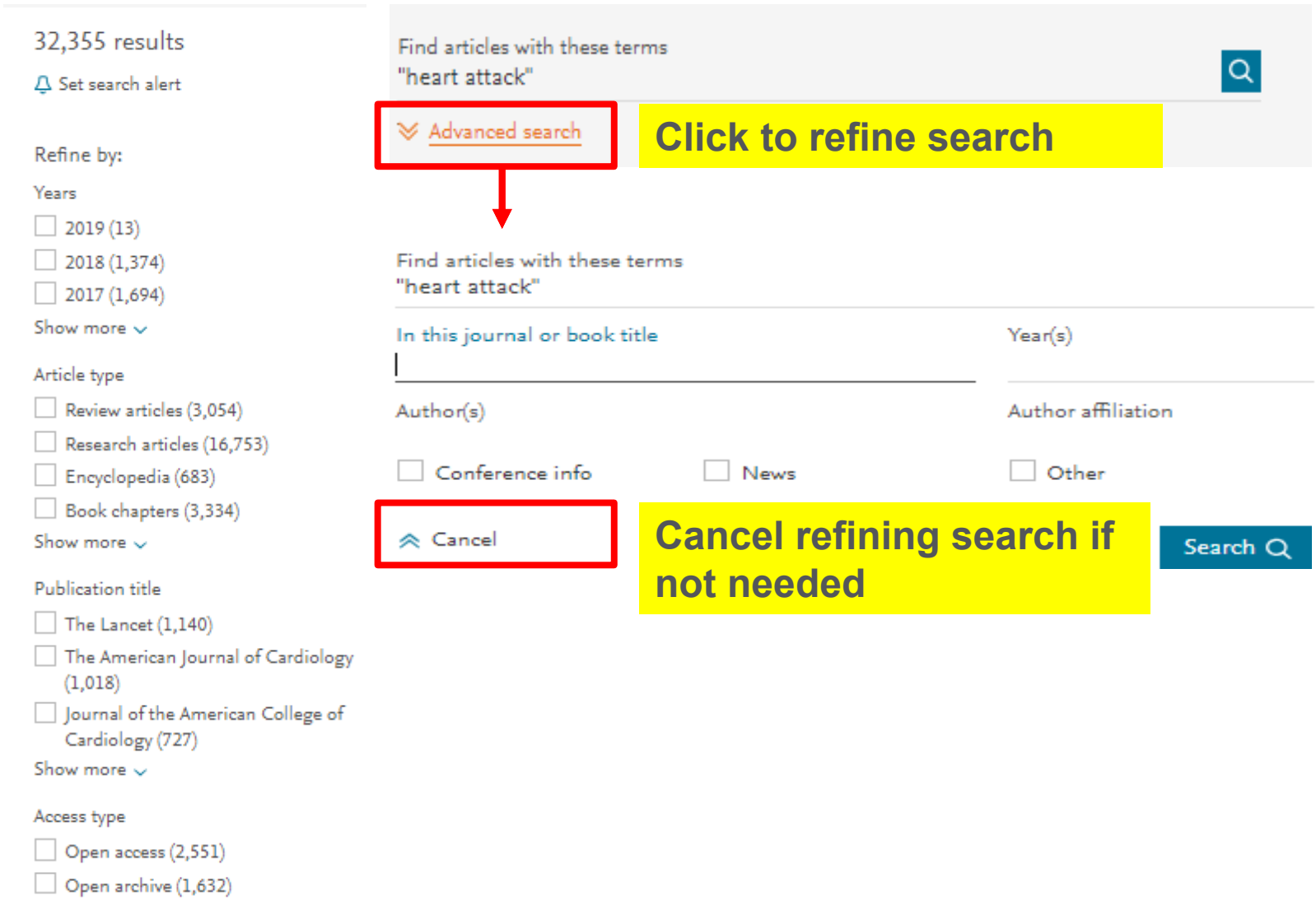

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chronic conditions, limitations, etc.) or the development of illness (i.e., disease incidence). Only a handful of studies examine the role of marital status after the onset of illness (Burnley, 1999, Chandra et al., 1983, Kilpi et al., 2015, Lammintausta et al., 2013, Nielsen and Mard, 2010) and no existing studies consider which aspects of the marital life course are important to survival after a

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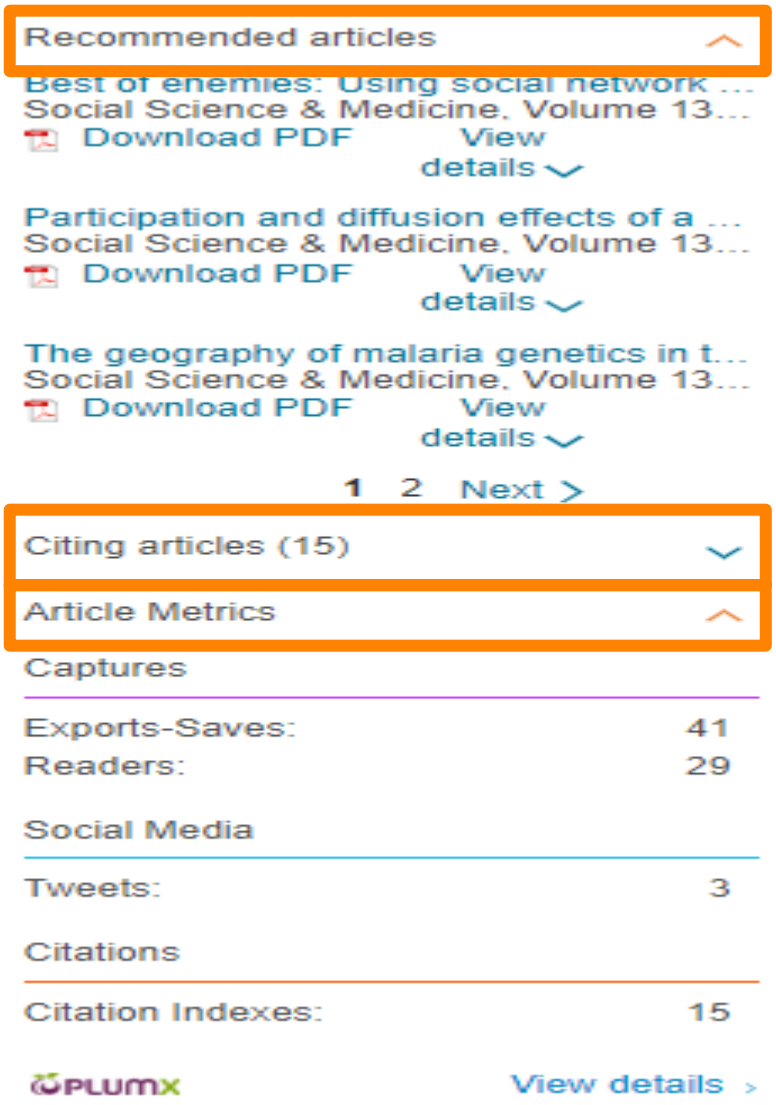

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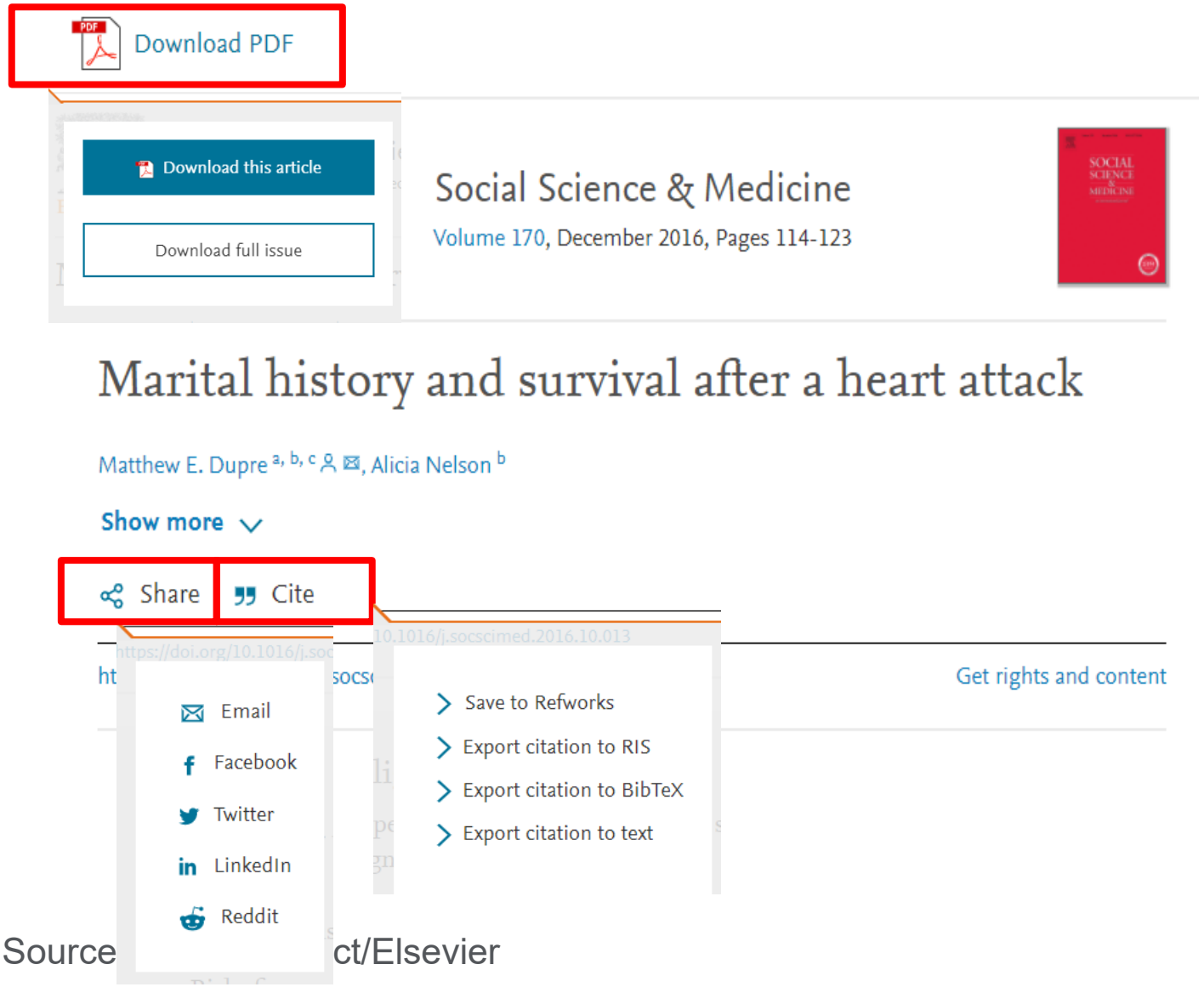

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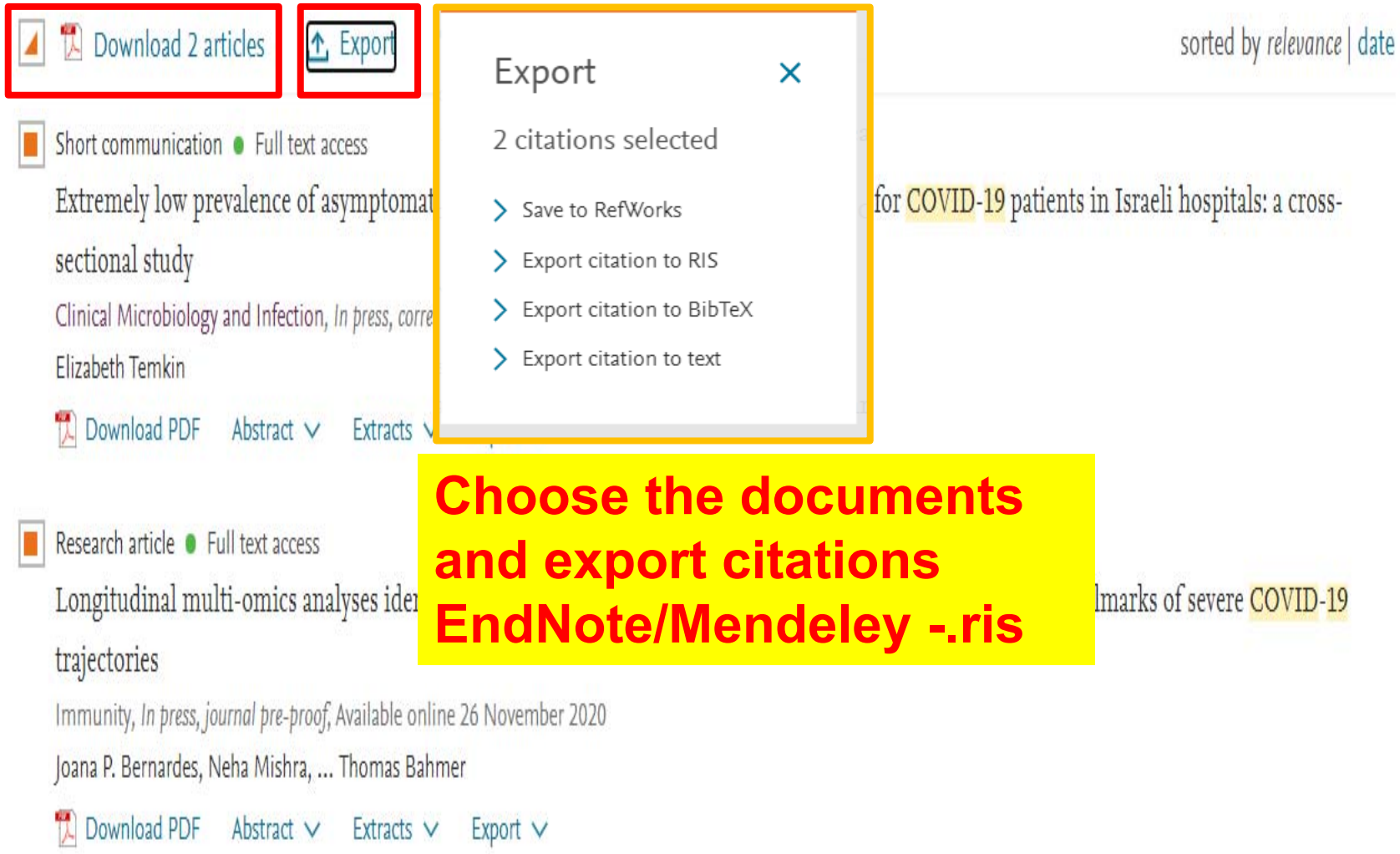

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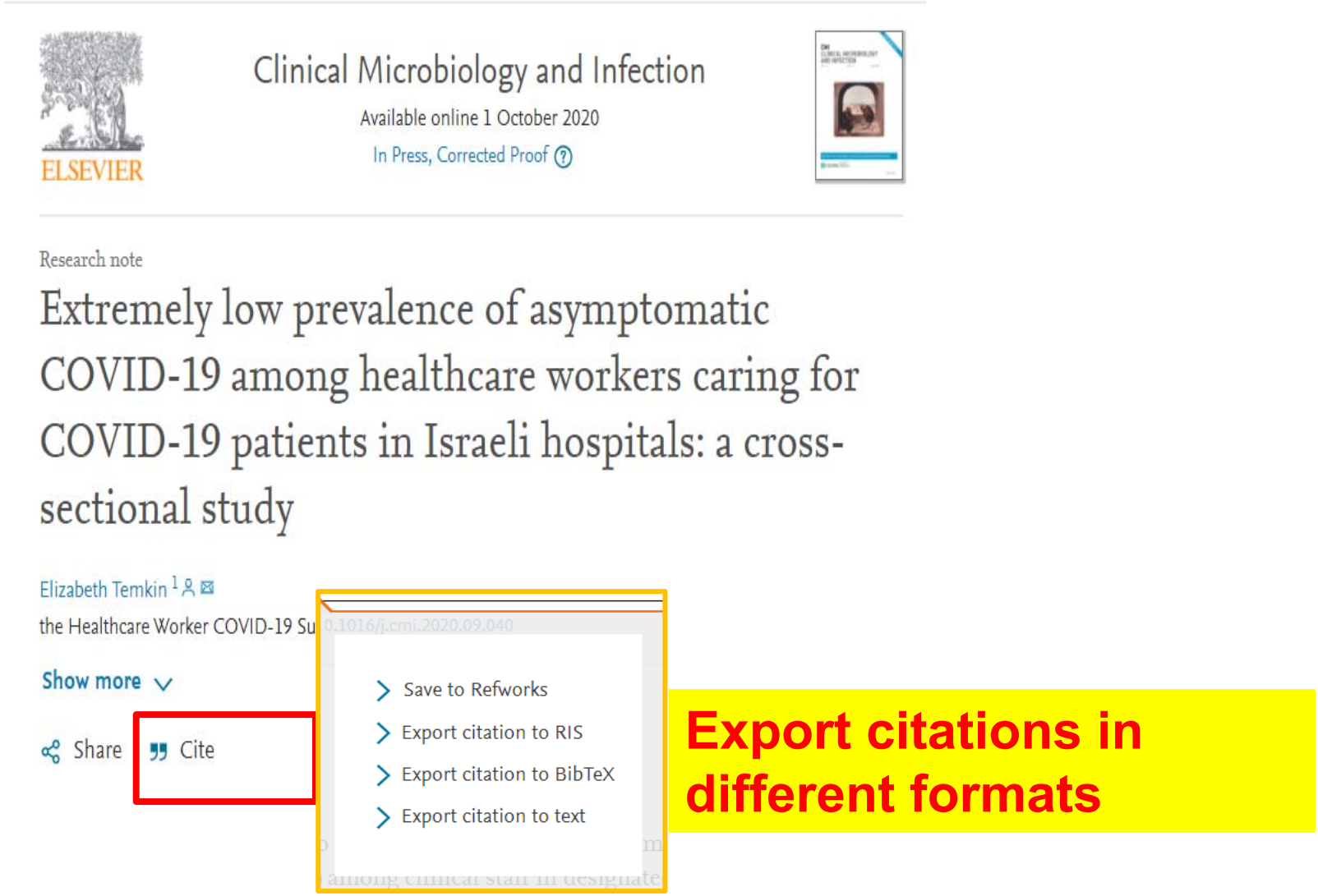

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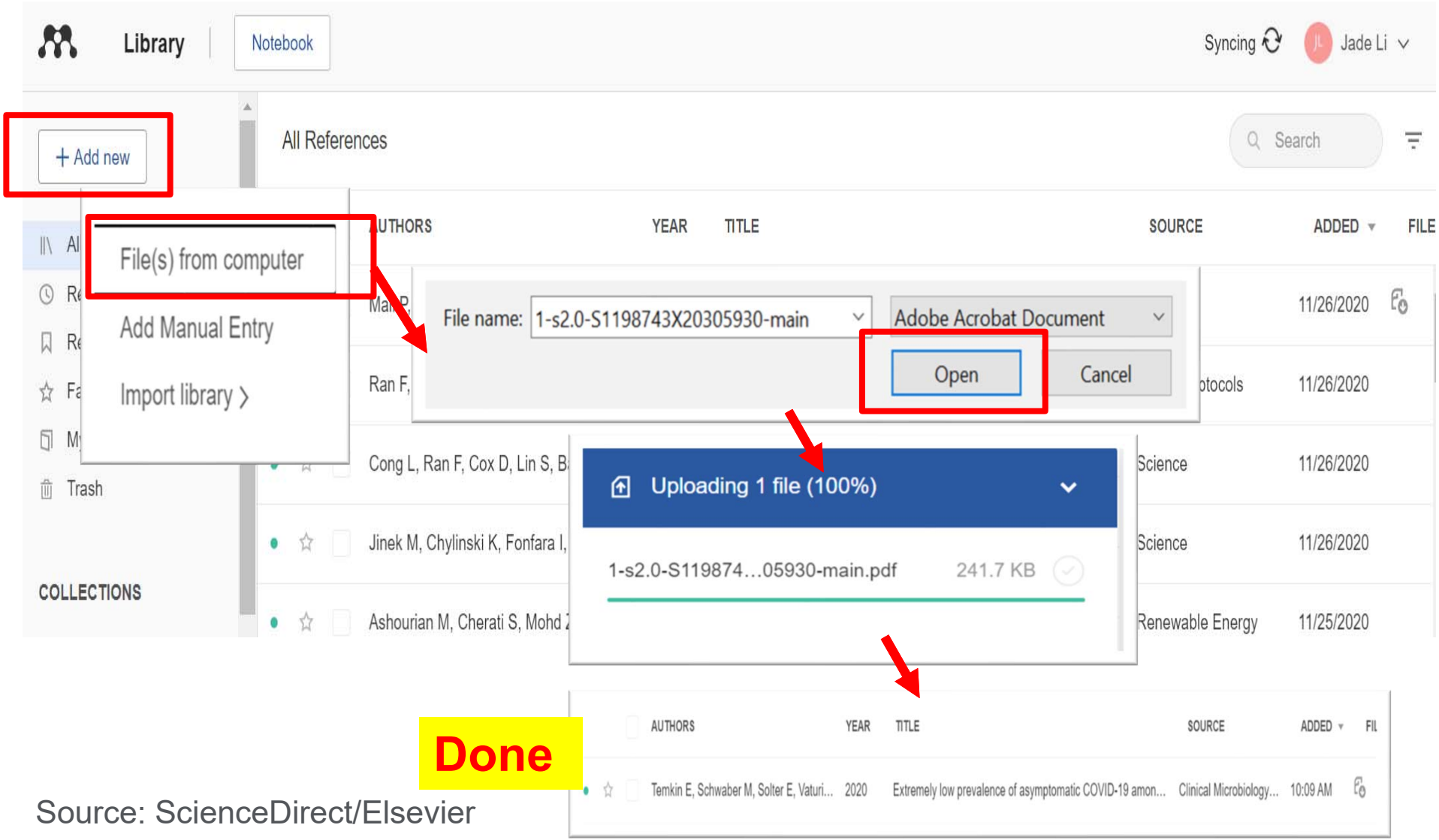

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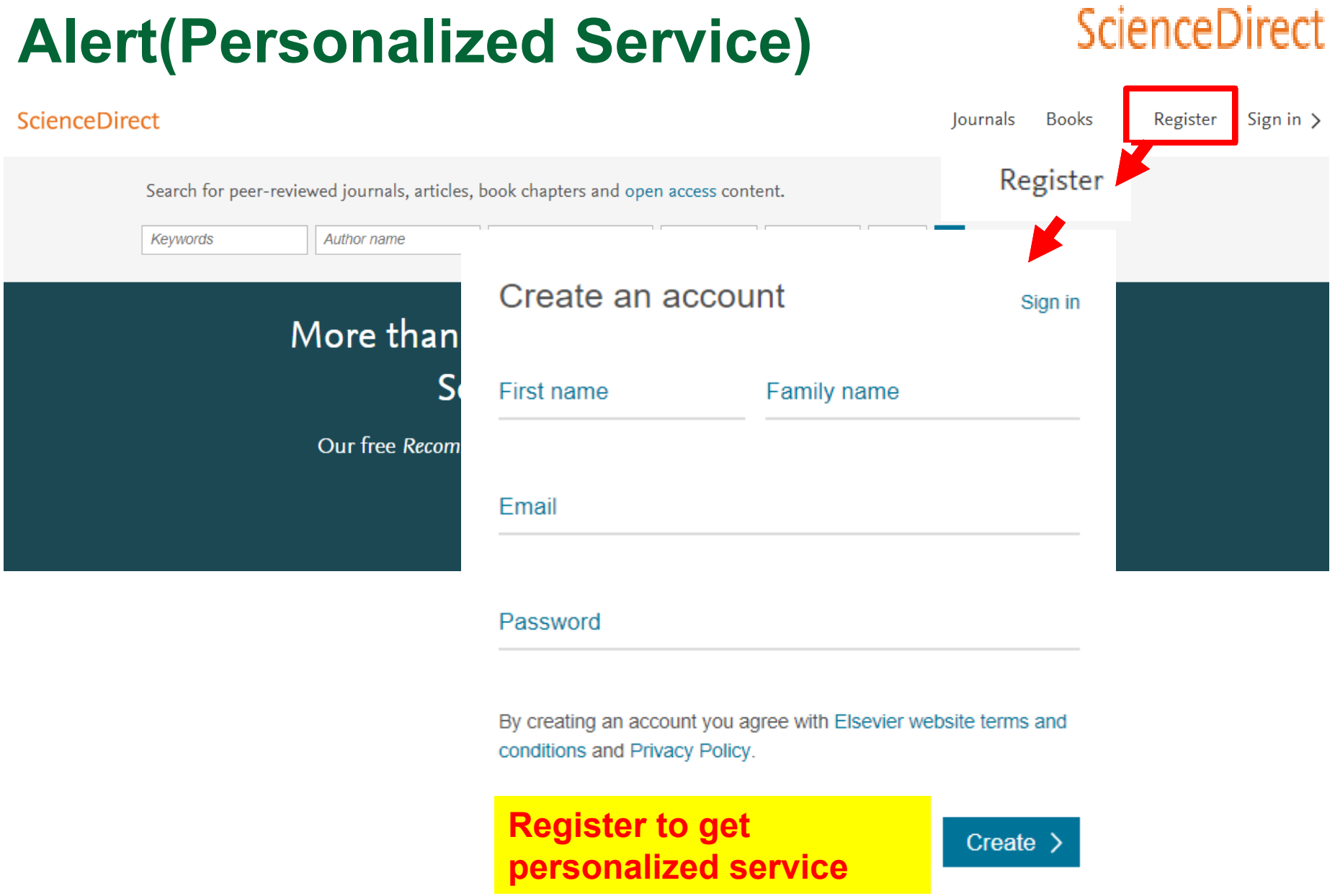

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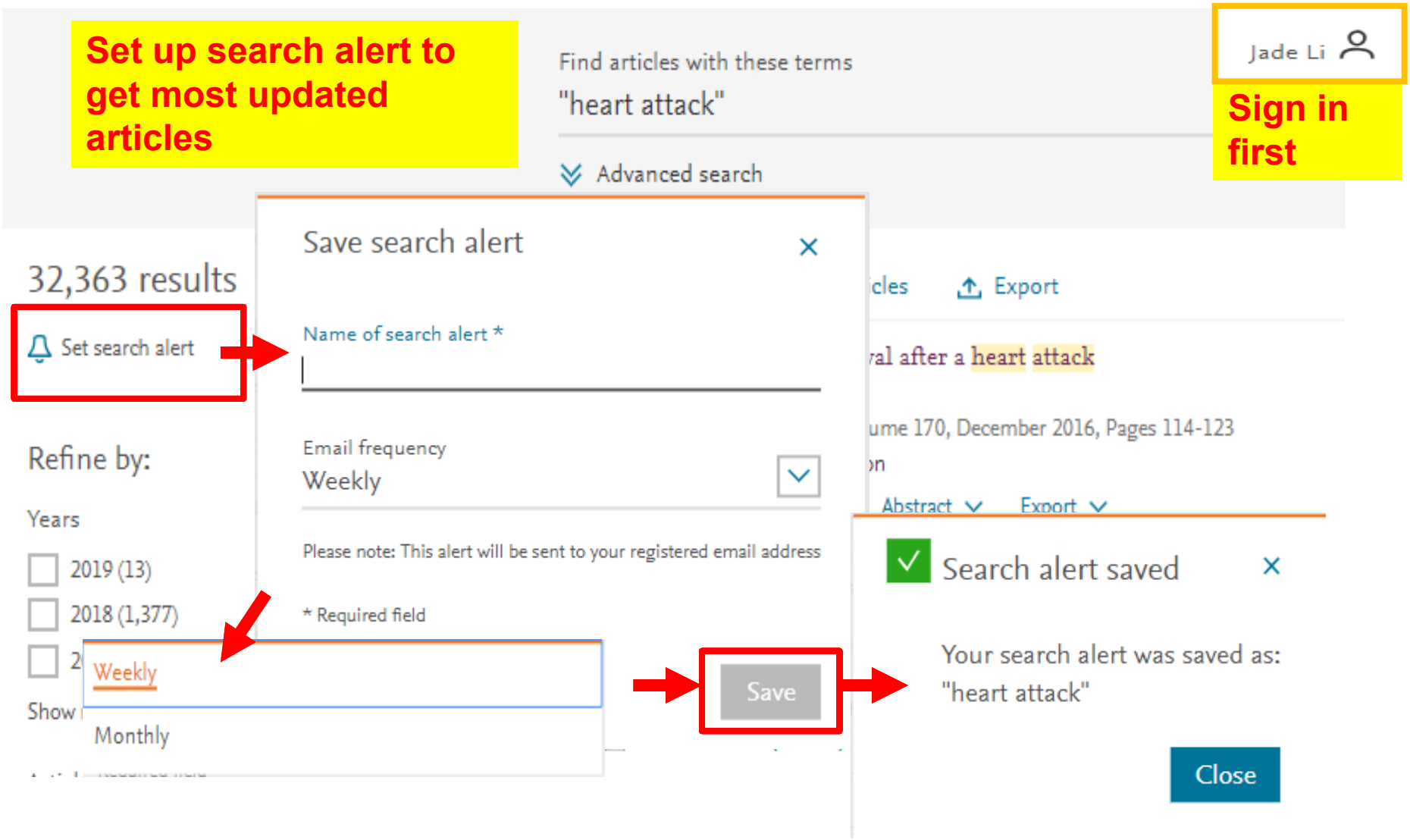

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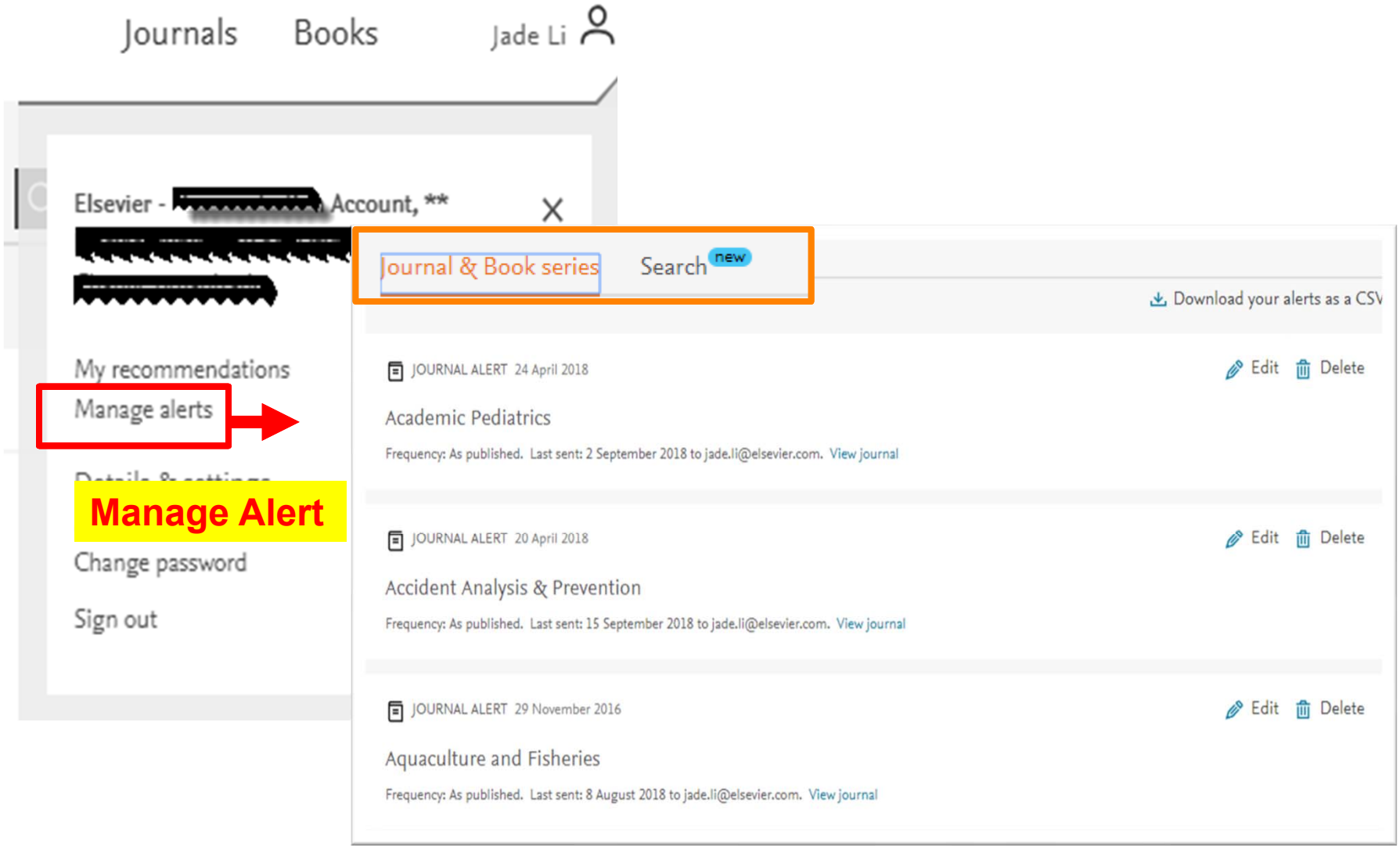

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