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A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis

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Introduction

Fibromyalgia syndrome is characterised by chronic widespread pain, sleep disturbance, fatigue and cognitive impairment, which have a major impact on quality of life [1, 2]. Symptoms include tender and stiff muscles, joints and tendons with multiple tender points, which are often extremely painful to touch [3] without grossly demonstrable tissue inflammation, deformity, or damage [4]. The underlying etiology of fibromyalgia is yet to be fully elucidated. Dysfunction of the central, autonomic and peripheral nervous systems, alteration of neurotransmitters, endocrine and immune systems, external stressors and psychological aspects have been implicated in the common symptom of widespread pain in fibromyalgia. There continues to be debate around the relative contributions of the central nervous system (CNS) and peripheral nervous system (PNS) in the pathogenesis of fibromyalgia [5]. Disturbed pain processing with central sensitisation,
identified by increased responsiveness to stimuli has been demonstrated in fibromyalgia. Increased central hyperrexcitability including wind up of ascending pathways has been implicated in the generation of widespread pain in fibromyalgia [6, 7]. A meta-analysis of magnetic resonance imaging (MRI) based studies (voxel-based morphometry, functional MRI, or resting state-MRI) in fibromyalgia showed region-specific changes in grey matter volume, a decreased functional connectivity in the descending pain-modulating system, and increased activity in the pain matrix related to central sensitisation [8]. However, the temporal relationship of CNS pathology and whether it is a primary defect in fibromyalgia, remains to be established. Other evidence suggests neurotransmitter abnormalities in fibromyalgia are central to the development of pain including elevated insular glutamate, abnormal dopamine response to pain and transmission and metabolism of serotonin leading to dysregulation of pain processing [7,16]. Despite these findings, there is no single unifying CNS pathology present in fibromyalgia that defines this widespread pain state. While there is no diagnostic gold standard, small nerve neuropathy (SFN) is currently defined as pain and or par-/or dyesthesias accompanied by findings of small nerve impairment in at least two of the following three tests: neurological examination, quantitative sensory testing, and skin punch biopsy and exclusion of relevant large fibre neuropathy [17]. SFN results in selective impairment of unmyelinated C and thinly myelinated Aδ fibers that mediate pain, heat, and cold sensation. Therefore, pathology of small nerve fibers remains a biologically plausible explanation that may at least contribute to the fibromyalgia symptom complex. Indeed, there is a significant sensory symptom overlap in approximately 20 – 35% of patients with painful neuropathy, suggesting a peripheral neuropathic origin in a subset of people with fibromyalgia [18]. Fibromyalgia has neuropathic pain features, which is often stimulus dependent with hyperalgasia and also exhibits allodynia often in the form of burning or prickling sensations; pain attacks are frequently described [18–21]. Decreased detection thresholds for noxious stimuli such as heat and cold have been demonstrated on quantitative sensory testing [22, 23]. Phenotypic similarities with other peripheral neuropathic pain disorders suggest the underlying mechanism for these symptoms may be of small nerve fiber origin [24], particularly in a subset of individuals. Recently, reduced intra-epidermal nerve fiber (IENF) density (IENFD) has been demonstrated after a sustained increase in insular glutamate in an experimental model of fibromyalgia, suggestive of an underlying pathogenic neuromplastic process [25]. Several studies in recent years have demonstrated significant small fiber pathology (SFP) in individuals with fibromyalgia [26–33], with a reduction in IENFD [26, 28–30, 33]. Other studies have also demonstrated SFP using corneal confocal microscopy (CCM) [31, 32]. However, SFN needs to be distinguished from SFN in fibromyalgia as the underlying mechanisms causing pathology in small fibers remains to be elucidated and the clinical phenotype of fibromyalgia is distinct from SFN [34]. Furthermore, in a study from the Netherlands the actual prevalence of SFN in the general population was 52.95 cases (60.9 male/45.4 female) per 100,000 inhabitants [35]. The actual background prevalence of pure SFN is significantly lower [36] than SFN in fibromyalgia [26, 28–33].

The aim of this study is to determine the prevalence of SFP in fibromyalgia through a systematic literature review and meta-analysis of published data which have used an objective assessment of small nerve fibers.

Methods

Search strategy

In accordance with PRISMA guidelines, protocol for this systematic review and meta-analysis was developed and subsequently registered with PROSPERO, (CRD: 42018087277). Electronic literature searches of MEDLINE (access via OVID), EMBASE (access via OVID), PubMed, Web of Science, CINAHL and the Cochrane Library were performed for articles reporting fibromyalgia and SFP. The searches were restricted to English language from inception to April 2018. A qualified medical librarian and R.G independently searched the stated databases using varying combinations of the following search terms: 'fibromyalgia', 'fibrositis', 'fibrosis', 'muscular rheumatism', ‘musculoskeletal pain syndrome’, ‘nonarticular rheumatism’, ‘periarthritis fibrositis’, ‘rheumatoid myositis’, ‘tension myalgia’, ‘myalgia’, ‘small fibre/fiber neuropathy’, ‘peripheral neuropathy’, ‘polynepathy’, ‘painful neuropathy’, ‘small fibre/fiber sensory neuropathy’, ‘small fibre/fiber pathology’ and ‘neuropathy’.

All the search results were combined using Endnote and duplicates were removed by R.G. Reference lists of the primary and secondary literature were manually browsed to identify any additional studies.

Inclusion and exclusion criteria

Studies were included if they (1) were original studies displaying prevalence data for SFP within a fibromyalgia population, (2) concerned adult patients with fibromyalgia diagnosed in accordance with international (American College of Rheumatology) ACR diagnostic criteria [36–38]; (3) included assessment of small nerve fibers in all patients, using skin biopsy, corneal confocal microscopy, laser Doppler imaging (LDI flare), microneurography or quantitative sudomotor axon reflex testing (QSART) 4 were reported in full-text publication. Studies were excluded if they, (1) were not a human study, (2) did not report SFP prevalence within fibromyalgia patients or (3) were not in English language. Only studies using quantitative structural or functional measures of small nerve fiber integrity were included within the systematic review as they objectively quantify small nerve fiber deficits. This is in contrast to alternate methods, which do not localise pathology directly to small nerve fibers i.e. thermal threshold testing. Fibromyalgia was defined in relation to either the 1990 or 2010 ACR criteria as ‘widespread’ pain, lasting for a period of 3 months or longer, in association with tender points or somatic symptoms as described in their respective protocols.

Two reviewers, (R.G. and K.E.) independently screened all articles and selected those that satisfied the inclusion criteria for full text analysis. The titles and abstracts of articles were screened to remove irrelevant studies and the remaining shortlisted articles were screened in depth for eligibility. The full texts of relevant articles were retrieved, screened and selected using the inclusion and exclusion criteria to compile a set of final articles to be reviewed. Both reviewers made a decision to include or exclude and any discrepancies were put forward to the senior author (U.A.) for final judgement on the inclusion of a study. The process of screening and selection for inclusion were recorded using a PRISMA flowchart (Fig. 1). Before data extraction and quality assessment U.A screened all articles in order to confirm their eligibility within this study.

Data extraction and quality assessment

Study characteristics, methodology data and results from studies were extracted independently by R.G. and K.E. and any discrepancies between the R.G. and K.E. were reviewed by U.A. Extraction of the first author, study name and country were completed. Subsequently followed by the sample size and participant number within each study group, age, sex, SFP diagnostic technique used, international guideline of fibromyalgia diagnosis and the prevalence number or estimation. The combined extracted data was reviewed by U.A. to ensure accuracy of the data extraction.

The articles were all appraised using a risk of bias tool specifically addressing external and internal validity of the selected studies. In
We have included comparative images (Fig. 2A–C) of IENF in a healthy-volunteer control, a person with fibromyalgia without SFP and a person with fibromyalgia and SFP. We have also included CCM images (Fig. 2D–F) of a healthy-volunteer control and people with fibromyalgia and SFP. This shows SFP as imaged by these two diagnostic modalities.

Data analysis

Each article selected for final analysis was included within a meta-analysis to determine the overall prevalence of SFP in fibromyalgia. Studies were weighted according to the prevalence effect size and the inverse of the study variance in order to generate an I² value, serving as a measure of heterogeneity among the studies. I² is a measure of inconsistency within the studies’ results [49] and reports the percentage of variation amongst studies that is due to heterogeneity and not chance [50]. The meta-analysis was conducted using a generic inverse variance outcome. The prevalence estimate of each study was used as the effect estimate, and the corresponding standard error (SE) for each study was calculated. The SEs for prevalence (p) estimates were derived from the equation \(\sqrt{p(1-p)/n}\), where n is the number of participants with completed data in study. Random-effects model were used to generate summary prevalence data displayed (on forest plots) with 95% CIs in view of the higher I² value (>50% for overall pooled data and subgroup analyses). In addition, individual subgroup forest plots were formed for diagnostic quantitative assessment used in the final selected studies. This also enabled the differences in prevalence estimates between each assessment method to be observed. A funnel plot was created to show possible bias within the meta-analysis results (supplementary material).

All statistical analyses and figure production were undertaken using Review Manager 5.3 (The Cochrane Collaboration, London, UK).

**Fig. 1.** PRISMA flowchart demonstrating the article screening process.

**Fig. 2.** IENF and CCM images in a healthy volunteer (A, D), a person with fibromyalgia (B, E) showing SFP and a person with fibromyalgia (C, F) showing no SFP. CCM – corneal confocal microscopy, IENFD – intra-epidermal nerve fiber density, FM – fibromyalgia, SFP – small fiber pathology. Permission sought and granted for Fig. 1 from: Üçeyler N, Sommer C. Small nerve fiber pathology. In: Perrot S, Hauser W, eds. Fibromyalgia Syndrome and Widespread Pain: From Construction to Relevant Recognition. Philadelphia, PA: Wolters Kluwer Health; 2019.

**Description of skin biopsy and CCM**

Skin biopsy technique was initially developed at the Karolinska Institute, Sweden and later standardised at the University of Minnesota and at Johns Hopkins University, USA [5]. Skin biopsy analysis of IENF are used for the diagnosis of patients with SFN through the identification of antibodies against protein gene product 9.5 (PGP 9.5). The immunoreaction is used to visualize the number and morphology of the dermal and IENF according to the European Federation of Neurological Societies (EFNS) [41]. A circular punch biopsy, 3–5 mm in diameter is rotated into the skin to obtain a cylindrical specimen which is then fixed, frozen and 50 μm sections are prepared and immunoreacted with antibodies against PGP 9.5 as a pan-axonal marker. IENF crossing the dermal-epidermal junction are counted to provide densities which are referenced against normative ranges to provide diagnostic cut off s [41].

CCM is a rapid non-invasive ophthalmic imaging modality which has been recently pioneered as a surrogate endpoint of peripheral neuropathy. The cornea is the most densely innervated tissue of the human body and receives sensory innervation from the trigeminal ganglion in the form of nerve bundles containing axons. These bundles terminate in the anterior cornea where they form a dense network of unmyelinated axons (19,000–44,000 axons within 90 mm² which are small nerve fibers) termed the sub-basal nerve plexus [42]. CCM can image these bundles of axons at 600x magnification. CCM quantifies axonal damage in early neuropathy [43], reliably [44], with high sensitivity and specificity [45, 46] and closely correlates to the severity of IENF loss [47, 48]. CCM methodology and assessment may be viewed in more detail at: [http://www.jove.com/index/Details.stp?ID=2194](http://www.jove.com/index/Details.stp?ID=2194).
Table 1
Data extraction information from all final selected studies.

| Author          | Country | Sample size | Study group              | Group size | Mean age (years ± SD or range) | Sex (Female/Male) | SFP diagnostic technique and criteria for diagnosis | International fibromyalgia guideline | Prevalence number | Prevalence estimate (%) |
|-----------------|---------|-------------|--------------------------|------------|-------------------------------|------------------|------------------------------------------------|----------------------------------|-------------------|------------------------|
| de Tommaso et al. [51] | Italy   | 81          | Fibromyalgia Control     | 21         | 51 ± 9                        | 18/3             | Skin biopsy: IENFD below the 5° percentile cut-off in the thigh, distal leg or finger-tip<sup>a</sup> | 2010 ACR criteria          | 16                | 76                     |
| Giannoccaro et al. [28] | Italy   | 52          | Fibromyalgia Control     | 20         | 40 ± 6                        | 19/1             | Skin biopsy: IENFD below 13.5 ENFs/mm in the thigh or 9.5 ENFs/mm in the distal leg | 1990 ACR criteria          | 6                 | 30                     |
| Kosmidis et al. [30]      | Greece  | 80          | Fibromyalgia Control     | 46         | 53 (29–76)                    | 41/5             | Skin biopsy: IENFD below 3.65 fibres/mm in the distal leg | 2010 ACR criteria          | 16                | 34                     |
| Leinders et al. [52]      | Germany | 116         | Fibromyalgia Control     | 28         | 51 (39–74)                    | 26/2             | Skin biopsy: IENFD below 6 fibres/mm in the thigh or distal leg | 1990 ACR criteria          | 14                | 50                     |
| Oaklander et al. [27]     | USA     | 57          | Fibromyalgia Control     | 27         | 47 (26–68)                    | 20/7             | Skin biopsy: IENFD below the 5° percentile cut-off in the distal leg<sup>a</sup> | 2010 ACR criteria          | 11                | 41                     |
| Oudejans et al. [31]      | Netherlands b | 39           | Fibromyalgia Control     | 39 b       | 39 (19–58)                    | 36/3             | Corneal confocal microscopy: CNFD (< 21.3 no/mm²), CNFL (< 12.7 mm/mm²), or CNBD (< 26.7 no/mm²). Values are below the 5° percentile cut-off. | 1990 or 2010 ACR criteria | 20                | 51                     |
| Ramírez et al. [32]       | Mexico   | 34          | Fibromyalgia Control     | 17         | 44 ± 5                        | All female       | Corneal confocal microscopy: CNFD (diagnostic cut-off unavailable) | 1990 or 2010 ACR criteria | 12                | 71                     |
| Öçzyler et al. [26]       | Germany  | 155         | Fibromyalgia Monopolar depression without pain Control | 24         | 59 (50–70) Mean age unknown (39–75) | 22/2             | Skin biopsy: IENFD below 8 fibres/mm in the thigh or 6 fibres/mm in the distal leg | 1990 ACR criteria          | 10                | 42                     |

<sup>a</sup> Precise cut-off values for IENFD not provided.

<sup>b</sup> Information are unavailable.

CNBD = corneal nerve branch density, CNFD = corneal nerve fibre density, CNFL = corneal nerve fibre length, ENF = epidermal nerve fibers, IENFD = intra-epidermal nerve fiber density.
Results

Study characteristics

After the removal of duplicates a total of 935 articles were generated from the electronic database and manual reference searches. A PRISMA flowchart was completed displaying the article exclusions at each stage of screening (Fig. 1). The titles and abstracts of 45 articles were screened using the inclusion and exclusion criteria. Analysis of 17 full text articles was performed in order to review eligibility and inclusion. Overall, eight articles satisfied the inclusion criteria and underwent data extraction (Table 1) and quality assessment (Supplementary material, Table 2).

Six studies were performed in Europe, [26, 28, 30, 31, 51, 52], one in the USA, [27] and one in Mexico, [32]. Studies had been described by the authors as case-control, cross-sectional or prospective. All studies used the 1990 or 2010 [36, 37] ACR Criteria for the classification of fibromyalgia as a standard definition.

Overall prevalence

The meta-analysis evaluated data from all eight articles, providing eight prevalence estimates; the estimated prevalence ranged between 30% and 76% (Fig. 3). Forest plot analysis showed the random-effects overall prevalence of SFP in fibromyalgia was 49% (95% CI: 38%, 60%) with a moderately high level of heterogeneity, \( I^2 = 68% \). Analysis of the overall funnel plot, (Supplementary material, Fig. 5) showed an equal but asymmetrical distribution of studies either side of the overall prevalence estimate.

Subgroup analysis

All selected studies diagnosed small fiber pathology in patients using either a skin biopsy \((n = 6)\) or corneal confocal microscopy \((n = 2)\). Skin biopsies were undertaken by; de Tommaso et al. [51], Giannoccaro et al. [28], Kosmidis et al. [30], Leinders et al. [52], Oaklander et al. [27] and Uceyler et al. [26]. The six prevalence estimates ranged between 30% and 76%, (Fig. 4). Analysis of the skin biopsy meta-analysis displayed a random-effects pooled prevalence of 45% (95% CI: 32%, 59%), with a moderately high level of heterogeneity, \( I^2 = 70% \). In comparison, Oudejans et al. [31] and Ramirez et al. [32] assessed SFP using corneal confocal microscopy. This meta-analysis, (Fig. 5) showed the random-effects pooled prevalence was 59% (95% CI: 40%, 78%), with a moderate heterogeneity, \( I^2 = 51% \).

Risk of bias

Evaluation of bias and article quality (Supplementary material, Table 2) showed the majority of studies had a low risk of bias. The Giannoccaro et al. [28] study displayed a moderate risk of bias. No sample size calculation was provided; only 20 fibromyalgia patients were studied and there were no details of ethnicity or the reasons for the chosen male/female ratio. Moreover, this study did not explicitly state a specialist or independent clinician reliably measured or reviewed the SFP diagnostic recordings, nor did this study display statistical analysis methods.

Discussion

This meta-analysis estimates a high prevalence of SFP, with 49% of people with fibromyalgia having a structural abnormality of the small nerve fibers and to our knowledge this systematic literature review is the first study to collate data on the overall prevalence of SFP in fibromyalgia. Based on the modified 2010 criteria, approximately 5% of the population are affected by fibromyalgia [53] and this equates to around 1.6 million people with SFP and fibromyalgia in the United Kingdom alone. Fibromyalgia has major implications on morbidity and patients experience a decline in their health-related quality of life with a significant economic burden on health services [54]. In our review, small fiber pathology was defined by objective tests which were either by skin biopsy or corneal confocal microscopy, both of which showed a high prevalence of SFP, challenging the current concept that fibromyalgia is largely a disorder of the CNS.

Fig. 3. Forest plot showing overall pooled prevalence estimates of SFP in fibromyalgia. de Tommaso et al. [51]; Giannoccaro et al. [28]; Kosmidis et al. [30]; Leinders et al. [52]; Oaklander et al. [27]; Oudejans et al. [31]; Ramirez et al. [32] and Uceyler et al. [26].

Fig. 4. Forest plot showing prevalence estimates of SFP in fibromyalgia in studies using skin biopsies. de Tommaso et al. [51]; Giannoccaro et al. [28]; Kosmidis et al. [30]; Leinders et al. [52]; Oaklander et al. [27] and Uceyler et al. [26].
We have strengthened our study by imposing strict criteria on the
diagnosis of SFP in a priori inclusion criteria with our study conducted
to PRISMA guidelines [55]. The tests for statistical heterogeneity
amongst articles suggested significant variability for overall pooled
data ($I^2 = 68\%$) and skin biopsy data ($I^2 = 70\%$) with moderate variability
in data from corneal confocal microscopy ($I^2 = 51\%$). Inconsistencies
in the classification of a positive SFP diagnosis between studies
may have contributed to the high heterogeneity. In the study by de
Tommaso et al. [51], skin biopsies were undertaken in three locations;
the thigh, distal leg and finger-tip. In contrast, Giannoccaro et
al. [28], Leinders et al. [52] and Üçeyler et al. [26] obtained samples
from the thigh and distal leg, whilst Kosmidis et al. [30] and Oak
lander et al. [27] obtained biopsies from the distal leg only. de Tommaso et al. [51], showed that 16/21 (76\%) patients with fibromyalgia
had an epidermal nerve density below the 5th percentile in at least
one site from the leg, thigh or finger-tip. Üçeyler et al. [26] showed a
reduction in IENFD and regenerating nerves stained using GAP43 in
both the thigh and distal leg of 24 patients with fibromyalgia. These
inconsistencies may limit the reliability of the prevalence estimate
and future standardised cut-off values for abnormal IENFD and in par
ticular corneal nerve parameters in fibromyalgia are warranted and
will allow for direct comparison in any future prevalence studies.

Abnormal CNS processing is evidenced in a number of studies in
fibromyalgia which have shown altered resting and stimulus-evoked
regional cerebral blood flow in pain and altered emotional processing
regions such as the thalamus, somatosensory cortex, insula, and ante
rior cingulate cortex [8, 56]. However, the reduction in grey matter
volume noted in fibromyalgia patients may be indicative of secondary
alterations in central neuroplasticity accompanying affective disor
ders [57]. Indeed in ‘classical’ SNF, brain networks tend to alter and
deconstruct into functionally independent components (reduced functional connectivity between the anterior cingulate cortex, amygdala and praeunceus), with severity being linked to the degree of
cutaneous nerve degeneration [58]. In other pain syndromes such as
dysmenorrhoea, patients exhibit adaptive/reactive hyperconnectivity
within the sensorimotor cortex [59]. In neither of these conditions is
there remains considerable scepticism about the relevance of these findings
for explaining the patients’ pain [51]; Indeed, it has been suggested
that some patients in whom fibromyalgia is diagnosed are instead
affected by SNF with clinical features mimicking fibromyalgia [69].
And in at least some patients, proximal fiber loss may be greater than,
or at least equal to, distal loss, configuring a non—length—dependent pattern more compatible with the wide
spread pain symptoms of fibromyalgia [69]. An experimental study of
Sprague Dawley rats, suggested that increased insular glutamate was
associated with a reduction in IENFD [25], thus implying that a central
neurotransmitter defect may contribute to SFP. However, we suggest
cautions in the translational value of an experiment with such small
numbers of animals to the human pathogenesis of SFP in fibromyalgia
[25].

The peripheral origins of pain are not in doubt in painful neuropa
thies, however, the question remains if central sensitization is the pri
mary driver in fibromyalgia. SFP also alters small blood vessel
function through altered neuropeptide response and upregulation of
$\alpha$-adrenergic receptors [70]. This neurogenic microvasculopathy may
explain at least partially, the skeletal muscle perfusion deficits, deep
pain, and exercise intolerance characteristic of fibromyalgia and a
number of other small fiber neuropathies [71, 72]. This microvascu
lopathy mediated by small nerve fibers may also contribute to the
common symptom of ‘brain fog’ and provide a putative mechanistic
link [73].

There was a limited opportunity to investigate the sources of
heterogeneity due to the small number of studies included and
lack of recorded patient’s characteristics, we therefore only com
pleted a stratified analysis based on the diagnostic modality of SFP.
Our study was limited to published data and English language pub
lications which may introduce respective bias. Furthermore, only a
single point assessment of small nerve fibers was undertaken in the
included studies; however, small nerve fibers degenerate and regen
erate [74, 75] and therefore may alter over time. Another limi
tation of our review was that none of the studies included for
prevalence estimates were primarily designed to produce prevale
nce data and is reflected in the relatively small sample sizes in the
included studies (largest study, $n = 47$). Only one study [27]
performed a sample size calculation to ensure that adequate
numbers were recruited. Two studies recruited from a single cen
tre, namely de Tommaso et al. [51] and Kosmidis et al. [30], thus
presence of population bias with an unrepresentative sample is a
distinct possibility.
The pooled prevalence estimates were higher with CCM suggesting it may be a more sensitive measure of SFP. CCM quantifies early axonal damage [43], reliably [44], with high sensitivity and specificity [45, 48] and closely correlates to the loss of IENF [47, 48]. As CCM is a rapid, reiterative, non-invasive imaging modality of small nerve fibers it may provide an ideal method to accurately define the prevalence of SFP in large population studies. Larger dedicated prevalence studies are required to augment this meta-analysis and accurately define the contribution of SFP in fibromyalgia. In particular, SFP prevalence in fibromyalgia needs to be determined stratified on the basis of duration of disease which will provide a significant insight in the natural history of this chronic pain condition.

Conclusion

Our meta-analysis shows that the prevalence of SFP in fibromyalgia is 49%. Fibromyalgia and chronic pain has a huge negative impact on quality of life and reduces the ability of our patients to work and function. There needs to be a significant improvement in the understanding of pain in fibromyalgia and the relative contribution of SFP in relation to pain needs to be established.

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Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.sermarthrit.2018.08.003.

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