Mounier-Kuhn syndrome: a systematic analysis of 128 cases published within last 25 years

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Abstract

Background and Aims: Mounier-Kuhn syndrome is a rare disease with abnormal enlargement of major airways, but epidemiological studies are lacking, and currently the most available data about it come from case reports, making it difficult to collate changes in a particular patient to those in previously published cases.

The aim of this work is to systematically review cases published in the last 25 years and to use descriptive statistics to summarize the patient demographic and clinical information therein in order to acquire details about patient clinical characteristics.

Methods: Cases published in world literature between 1987 and 2013 were sought and reviewed according to PRISMA guidelines. Cases were included only if patient's age was at least 18 years, and a computed tomography scan with tracheal measurements was available.

Results: An 8:1 male predominance was found in 89 identified reports (128 cases). Mean age was 53.9 years, and average tracheal diameter was 36.1 mm. No correlation between increasing age and increasing tracheal diameter was found. Bronchiectasis, tracheal diverticulosis and tracheobronchial dyskinesia were common (49.2%, 33.6% and 28.9%, respectively). Cough, dyspnea and recurrent respiratory infections (71.1%, 51.6% and 50.8%, respectively) were the most common complaints.

Conclusions: The data confirm that syndrome mostly manifests with nonspecific respiratory symptoms and is significantly more common in males. Importantly, there was no connection between age and airway diameter, a fact that could mean that the enlargement does not progress over time, and its severity depends on some other yet undetermined factors.

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The author has stated explicitly that there are no conflicts of interest in connection with this article.

Abbreviations:
COPD chronic obstructive pulmonary disease
CT computed tomography
MKS Mounier-Kuhn syndrome

Introduction

The Mounier-Kuhn syndrome (MKS), the first case of which was described in 1937 (1), is a rare, most likely congenital syndrome, whose main characteristic is an enlarged trachea and main bronchi. In 1988, the first visualizations of MKS in computed tomography (CT) were described (2, 3), and although numerous case reports are published every year, there have been very few attempts to summarize them (4–6).

To the best of the author's knowledge, there is no review available that has systematically tried to identify

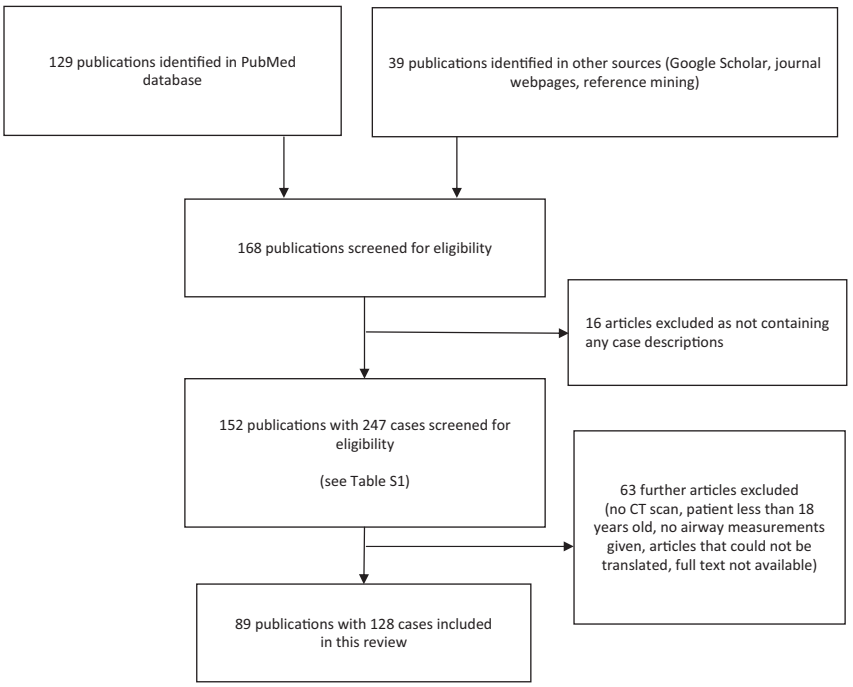

Figure 1. PRISM flowchart of case selection.

the published cases and that would have performed a statistical analysis of them. Although individual case reports and previously published reviews do provide information about disease characteristics, symptoms and already implemented treatment strategies, they do not provide the overview of an issue when it is needed. As of MKS it is currently unclear when the dilation of the airways start and if (or how) it progresses over time. Patients usually present themselves with a marked dilation, but the frequently asked question 'whether the dilation will increase further?' currently cannot be answered.

Therefore, the aim of this review is to clarify the clinical characteristics of the MKS demographics and symptoms by systematically searching and reviewing cases published within the last 25 years, according to the PRISMA guidelines for systematic reviews (7).

Materials and methods

PubMed, ScienceDirect and GoogleScholar databases were searched for publications of MKS case reports by using terms 'Mounier-Kuhn syndrome', 'tracheomegaly', 'bronchomegaly' and 'tracheobronchomegaly'. Time was restricted to cases published between January 1987 and December 2012. Articles in Japanese, Chinese and Korean were excluded as it was not possible to translate them. Additionally, the web pages of the five most influential journals of respiratory medicine (as listed by online SCIMAGO journal rank (8): *American Journal of Respiratory and Critical Care Medicine*, *European Respiratory Journal*, *Chest*, *Thorax* and *Proceedings of the American Thoracic Society*) were reviewed for meeting and conference supplement not published elsewhere. References of acquired articles were screened for additional publications.

The full texts of the articles identified by the search were retrieved and reviewed for conformity with the following inclusion criteria: patient was older than 18 years; tracheo- or bronchomegaly was confirmed with a CT scan according to the criteria published by Breatnach *et al.* (9) [the criteria originally were developed for use with conventional chest X-ray, and later validated for CT by Roditi and Weir (10)]; and at least one abnormal tracheal or bronchial measurement clearly was given in the publication.

Conference abstracts were included only if no subsequent publication of the particular case could be found and if the case met all inclusion criteria mentioned above. For the flowchart of case selection, see Fig. 1. Information about the demographics of the patient, smoking history (pack years were calculated if data were available), airway size, patient's complaints and lung ventilation function was searched for in the case reports that were included. After the data collection was completed, in a small random sample of 13 cases (10%), the gathered information was compared

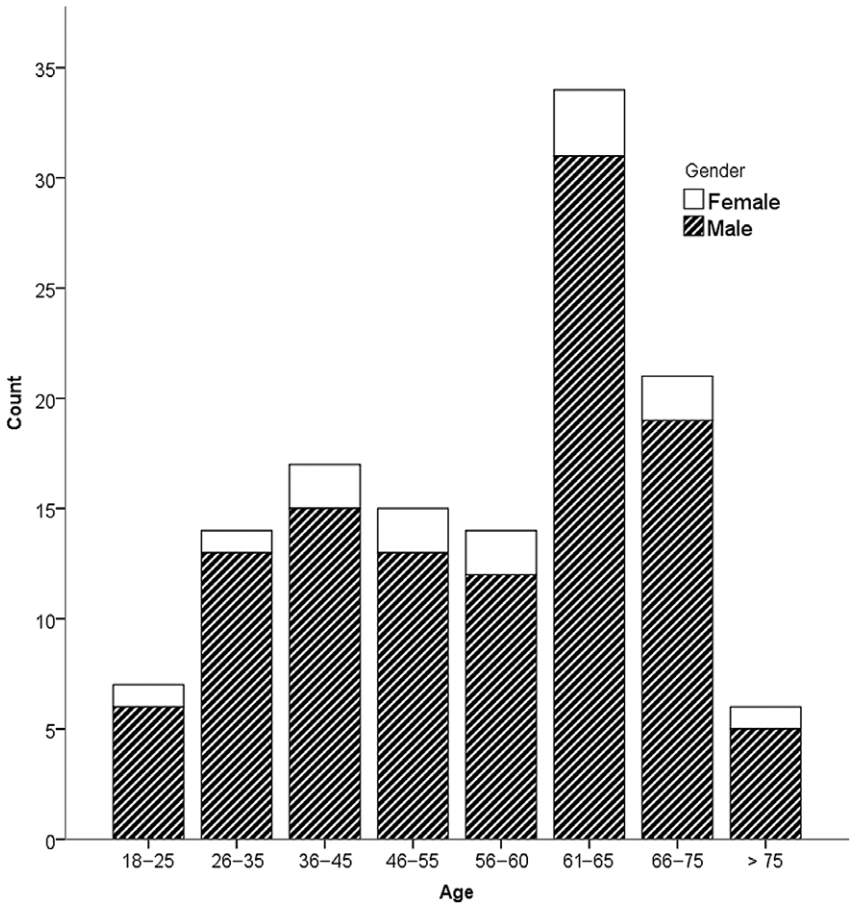

Figure 2. Age and gender frequencies for patients diagnosed with Mounier-Kuhn syndrome (MKS).

once again with the case reports to check for accuracy – no errors were detected. The final data table was analysed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA) computer program. Acquired data were checked for normality and depending on the results either parametric (Student's *t*-test, Pearson's coefficient of correlation) or nonparametric tests (Mann–Whitney *U*-test, Spearman's rank correlation) were applied. Results of calculations were rounded to one decimal place. Where information was missing the available data was summarized.

Results

The search in PubMed identified 129 publications since 1987, and 39 additional publications were found with other methods, with both groups mentioning 173 and 74 cases of MKS, respectively (247 cases in a total of 168 publications). Sixteen publications were excluded as the full text of the article could not be acquired. An additional 63 publications did not meet the inclusion criteria, leaving 89 publications (covering 128 patients) for review. A full list of identified cases (with reasons for exclusion, where applicable) may be found online at the publisher's website.

There were 114 (89,1%) male and 14 female (10,9%) patients (a ratio of 8.1:1). The distribution of age (Shapiro–Wilk test, $P = 0.000$) and other continuous variables were found to be nonnormal; therefore, nonparametric tests were used for analyses. The average age was 53.9 years, and males were slightly younger than females (53.8 vs 54.9 years, respectively), but this difference was not statistically significant ($P = 0.7$, Mann–Whitney *U*-test). Fig. 2 shows number of patients per age group. Further details about the age distribution can be seen in Table 1.

The average tracheal size was 36 mm (median and mode 34 mm, min 25 mm, max 65 mm). There was no correlation between the patient's age and tracheal and/or bronchial diameter, but a weak correlation could be observed between the tracheal and/or bronchial diameter and the duration of disease (as defined by the length of complaints, $\rho = 0.22$, $P = 0.045$). In 29.7% ($n = 38$) of the cases only the tracheal dimensions were published, and in another 25.8% ($n = 33$) only the trachea was enlarged. In this subgroup with

Table 1. Patient characteristics

	Females	Males	In total
	14 (12%)	114 (88%)	128 (100%)
Reporting hospital (region)	% of females	% of males	
Europe	57.1% (8)	33.3% (38)	35.9% (46)
North America	35.7% (5)	39.5% (45)	39.1% (50)
Other	7.1% (1)	27.2% (31)	24.9% (32)
Age, years			
Mean	54.9	53.8	53.9
Median	60.5	60	60
Mode	62	62	62
Youngest	25	20	20
Oldest	79	86	86
Smokers, % (*n*)			
Existing	16.7% (1)	30.5% (18)	14.8% (19)
Former	33.3% (2)	27.1% (17)	14.1% (18)
Never	50% (3)	42.4% (25)	21.9% (28)
No data	57.1% (8)	48.2% (55)	49.2% (63)
Average tracheal diameter, mm*	33.2	36.5	36.1
Smallest	25	27	25
Largest	50	65	65
Average bronchial diameter, mm			
Left bronchus	20	23.4	*23.0*
Right bronchus	21.0	24.5	24.0
No data, % (*n*) cases	34.4 (44)	34.4 (44)	34.4 (44)
Tracheal diverticulosis noted in % (*n*) cases	64.3% (9)	29.8% (34)	33.6% (43)
Bronchectasis noted in % (*n*) cases	57.1% (8)	48.2% (55)	49.2% (63)
Tracheobronchial dyskinesia noted in % (*n*) cases	21.4% (3)	29.8% (34)	28.9% (37)
Chief complaints			
Cough	85.7% (12)	69.3% (79)	71.1% (91)
Dry	21.4% (3)	22.8% (26)	22.7% (29)
Productive	64.3% (9)	46.5% (53)	48.4% (62)
Recurrent respiratory infections	57.1% (8)	50% (57)	50.8% (65)
Hemoptysis	100% (14)	14.9% (17)	13.3% (17)
Dyspnea	57.2% (8)	50.9% (58)	51.6% (66)
Persistent	42.9% (6)	43% (49)	43% (55)
On exertion	14.3% (2)	7.9% (9)	8.6% (11)
Thoracic pain	100% (14)	7% (8)	6.3% (8)
Finger clubbing	7.1% (1)	10.5% (12)	10.2% (13)
Changes upon auscultation (wheezes, rhonchi, crepitation)	42.9% (6)	29.8% (34)	32.3% (40)
Unilateral	7.1% (1)	3.5% (4)	3.9% (5)
Bilateral	35.7% (5)	26.3% (30)	27.3% (35)
Fever	28.6% (4)	13.2% (15)	14.8% (19)

*Largest value of either coronal and sagittal sections used.

normal bronchial size, the average tracheal diameter was smaller – 32.2 mm ($P < 0.001$, Mann–Whitney *U*-test). In addition to enlargement of the airways (the hallmark change caused by MKS), bronchiectasis and tracheal diverticulosis were observed in 48.5% ($n = 64$) and 33.6% ($n = 43$) of the cases, respectively. At least 28% ($n = 34$) of the patients had tracheobronchial malacia (for this review, terms 'tracheomalacia' and 'dyskinesia' were considered to be equal), but it must be said that in most papers presence or absence of tracheal- or bronchial malacia was not mentioned.

In just 53.1% of the cases was it stated whether the patients were smoking or not ($n = 68$). In this subgroup, the average age of current and ex-smokers was statistically significantly higher than that of nonsmokers (53.9 vs 44.2 years, $P = 0.002$, Mann–Whitney *U*-test). Of all patients, 21.9% had never smoked. For 27 (21%) cases where the calculation of pack years was

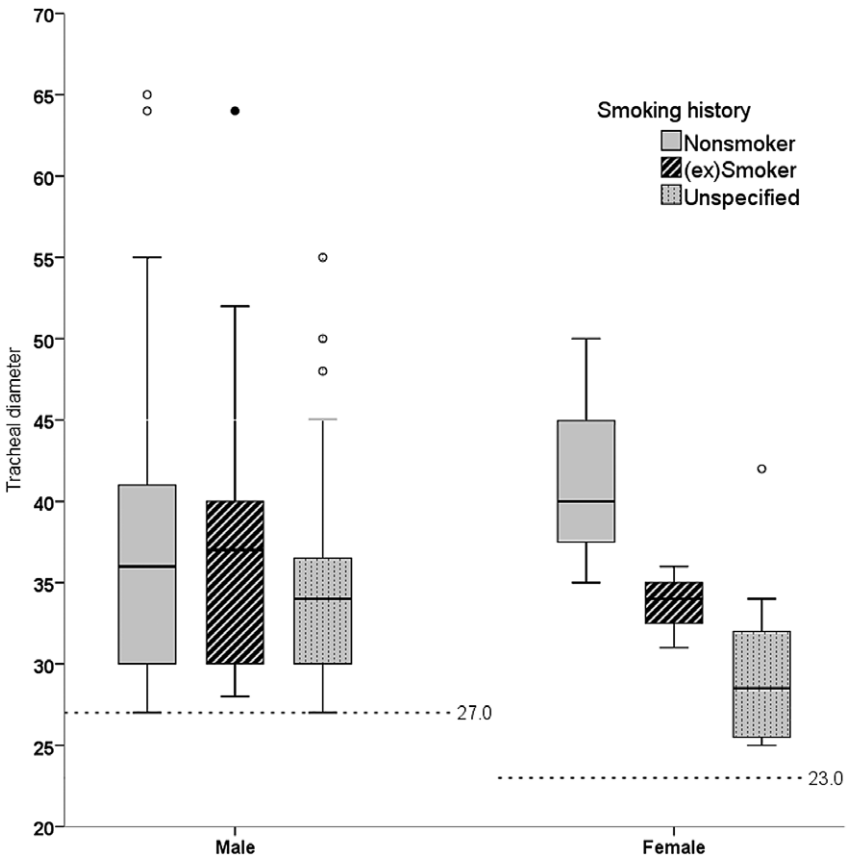

Figure 3. The average tracheal diameter in patients with Mounier-Kuhn syndrome (MKS) depending on their smoking history.

possible, the average quantity was 36 pack years (min 5 and max 80). In this small group, the number of pack years did not correlate with the tracheal diameter or with any of the patients' symptoms. See Fig. 3 for relationships between smoking history and tracheal diameter.

Information about spirometry test results was available for 33 (25.8%) patients, although the level of details varied from a simple statement about the type of changes (obstructive/restrictive) to a more detailed account of spirometry test results. The full summary is presented in Table 2. The majority of patients for whom spirometry data were available (48.5%, $n = 16$) had an obstructive ventilation defect, although a significant part had normal ventilation function (39.4%, $n = 13$).

Chronic obstructive pulmonary disease (COPD) had been diagnosed at some point in 25.8% ($n = 33$) of the patients. Of those patients, 10 were known to have smoked for some time or still smoked, 4 patients had never smoked and for 19 patients that had been diagnosed with COPD at some point no smoking history was available. Some patients (10.9%, $n = 14$) had received treatment for tuberculosis and in half of those cases, it was clearly stated that the presence of tuberculous bacteria was never found.

The average duration of symptoms was 14 years. Cough was the most frequent complaint (71.2%, $n = 91$), followed by recurrent respiratory infections (49.2%, $n = 63$) and persistent dyspnea (43.2%, $n = 55$). In just two cases (1.6%), it was clearly stated that the patients did not have any pulmonary complaints (11, 12) and the MKS was found accidentally.

Table 2. Lung function test results ($n = 33$)*

	Mild to moderate	Severe	Very severe
Normal	13 (39%)†		
Obstructive	3 (9%)	12 (36%)	1 (3%)
Restrictive	1 (3%)	1 (3%)	–
Mixed	–	2 (6%)	–
Not available	95 (74% of all patients)		

*GOLD Spirometry Guide 2010 (25) was used for classification where published results allowed that. Otherwise published type of change and severity was used, it was not possible to distinguidsh between mild and moderate cases.

†Percentages refer to 33 patients who had lung function test results.

Other common complaints and signs noted in the reports are summarized in Table 1.

Prognosis of MKS is unclear as the published reports mostly provide information about the patient only as seen at the point of diagnosis and lack follow-up data. In 10.9% ($n = 14$) of the cases, a lasting improvement with therapy was noted and in 5.5% ($n = 7$) case the disease progressed over time, including three cases (2.3%) where the patient died [in two of these of progressing respiratory failure (13, 14) and in the other of acute respiratory failure due to pulmonary embolism and subsequent nosocomial pneumonia (15)]. But it must be noted that of 10 cases where length of follow up was noted, in just two of them the follow up was 8 and 16 years, with an average of 2.2 years in remaining eight, so long-term data are not available.

Discussion

This work outlines the available clinical and demographic characteristics of MKS by using descriptive statistics. The average age, tracheal and bronchial dimensions, patients' smoking history and most common clinical symptoms have all been extracted and collected from the published case reports.

For comparison, the 30 cases reviewed by Johnston and Green in 1965 have the greatest value as they have not been included in the data collection of this review. Although not calculated by the authors, some simple descriptive values can be easily acquired from the publication (a single case of an eight-year-old boy from that publication has been excluded from the subsequent summary); 23 males and 3 females (a ratio of 7.6:1) were included, and for three patients the gender was not given, which is approximately the same gender ratio as in this study. The average age is 39 years (4), which is markedly less than the average of 54 years in this study (the largest three series of case reports identified in this study, accounting for 24% ($n = 31$) of the total number of cases, had average ages of 56.5 (16), 61 (17) and 62 (18) years). A likely cause of such a difference between the earlier review and this one is the overall increase in life expectancy as well as the availability of more effective treatment options in cases of severe disease.

Bateson *et al.* (19) in 1973 has noted that the MKS might be more common among patients of African-American descent. The majority (79.7%, $n = 102$) of the selected cases had not given any information on the subject, so the validity of Bateson's statement cannot be verified. Of the 26 patients (20.3% of all cases) where the ethnicity was mentioned, most (38.5%, $n = 10$) were Caucasians, four cases (15.4%) of MKS were reported in dark-skinned patients of various ethnic origin and another four (15.4%) had Hispanic origin.

Of all the cases, 81.2% ($n = 104$) had at least one tracheal measurement at or above 30 mm, which is abnormal regardless of the reference value used – possibly suggesting that subtle airway enlargement is rather unlikely. Tracheal diameter also tends to increase if the large bronchi are also involved – a possible sign of a more severe illness. But again, the lack of data in the case reports did not allow for a grading of severity of patients' symptoms. Additionally, among the excluded cases with no tracheal measurements, there were two with (presumably) isolated bronchomegaly (20, 21), the significance of which remains uncertain. The fact that increasing age does not correlate with tracheal or bronchial size could mean that once certain enlargement has taken place, the anatomical changes do not progress over time. What factors determine that remains to be seen. The extent of atrophy of longitudinal smooth muscle fibres that has been noted previously could be one of the determining factors.

The relationship between MKS and COPD is unclear. Both conditions share the same unspecific symptoms and significant proportion of patients with MKS have or have had a diagnosis of COPD. It seems plausible that MKS facilitates the development of COPD and subsequent bronchiectasis, but the mechanism of such course has yet to be established. Indeed, two previous COPD studies (22, 23) found the frequency of bronchiectasis to be 48.6% and 57.6%, which is quite similar as among MKS patients. But much better information about patients' smoking habits as well as about their occupation would be needed to ensure that COPD in patients with MKS is not caused by common environmental factors. The fact that nonsmokers were on average significantly younger than (ex-) smokers requires an explanation, which the author currently cannot provide. It would seem plausible that in the case of smokers, the symptoms tend to be attributed to their harmful habit and the development of COPD, whereas the nonsmokers, to whom such a common explanation cannot be applied, tend to be examined more thoroughly.

The MKS has been reported also in patients with different congenital and connective tissue disorders (6), but the number of cases published for each clinical entity is so small that it excludes all attempts to draw any conclusions about possible clinical relationship.

A previous paper gave a rough estimation of at least 300 published cases (6). It can now be updated to a more precise figure. This study found 247 cases, and Johnston and Green (4) identified 30 cases until 1965. By restricting a search in PubMed for the time span between 1965 and 1987, one can retrieve at least additional 80–85 titles, so it is reasonable to argue that at least 360 cases have been published so far. Some (24) have noted that a significant number of patients with MKS might be undiagnosed as they do not have any symptoms. But only two of the identified cases in this review were clearly asymptomatic patients, for whom diagnosis was made accidentally.

The value of this work lies in the fact that for the first time, the numerical values of published cases of MKS have been analysed. An estimation of average values of a patient with the MKS would help the reader to relate a patient with MKS in regards to other patients encountered by other and would be helpful in estimating the severity of the changes to airways, which is not possible by reading single case reports. Data presented here would also facilitate discussion with the patient, allowing for more concrete answers to patients' queries.

Apart from the restrictions imposed by the study type (a retrospective, case-based review), the most important other limitation is the large number or cases excluded from review (of the 247 identified cases 48.2% were excluded), which raises questions about the completeness of the data. The author of this review can only argue that whereas by relaxing the exclusion criteria some of the categories would gain additional data, most of the others would become only less complete, and therefore the integrity of the data table would not increase much. A number of cases even when recognized might altogether not reach the editorial offices if the treating physician is not interested to publish. Another major drawback is the lack of information and inconsistency in how the case is reported when a publication is available. Because of that, any subgroup analysis (especially regarding clinical parameters like ventilation function and common laboratory data) could deal with only a minority of included cases. So a previous recommendation can only be repeated that for diseases where large epidemiological or clinical trials are unlikely to be conducted, case reports should include as much demographic and clinical information as possible (6).

Conclusions

The results confirm that MKS mostly manifests with nonspecific respiratory symptoms and is significantly more common in males. In the author's opinion, the most important finding is the lack of connection between age and airway diameter, a fact that likely means that the enlargement does not change or progress much over time. But the reasons why the airway dilation is barely noticeable in some cases and so extensive in others remain unknown.

Acknowledgement

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Cases of Mounier-Kuhn syndrome published since 1987.