Original Article

A higher aneurysmal subarachnoid hemorrhage incidence in women prior to menopause: a retrospective analysis of 4,895 cases from eight hospitals in China

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Background: Subarachnoid hemorrhage (SAH) from a ruptured cerebral aneurysm is a devastating disease. Despite the risk factors, including hypertension, cigarette smoking and alcohol use, are more common in men, aneurysmal SAH belongs to a few diseases which the incidence is higher in women than in men. Sex hormones, especially estrogen, might be protective against this condition. Hormone replacement therapy (HRT) seems to be associated with a reduced risk for aneurysmal SAH. This study aims to know the prevalence of aneurysmal SAH of men and women at different ages.

Methods: The age and gender information of 4,895 case of aneurysmal SAH (3,016 females, 1,879 males) were collected retrospectively from eight institutions in mainland China. The prevalence of aneurysmal SAH of men and women at different ages was analyzed.

Results: The data showed women had a higher incidence of aneurysmal SAH than men starting at late thirties, and men might have a higher incidence of aneurysmal SAH than women only before 37-year-old.

Conclusions: Menopause may not be the only dominant factor causing higher incidence of aneurysmal SAH in women than in men.

Keywords: Physiological gender difference; epidemiology; aneurysmal subarachnoid hemorrhage; cerebral aneurysm

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Introduction

Subarachnoid hemorrhage (SAH) from a ruptured cerebral aneurysm is devastating. Its overall incidence is approximately 9 per 100,000 person-years (1-3). Incidences are higher in Japan and Finland, indicating a partial genetic role (2). Current medical management options in patients with unruptured cerebral aneurysms are limited, consisting largely of smoking cessation, blood pressure control, and neurosurgical or endovascular interventions (3). Decisions regarding optimum of unruptured cerebral aneurysm management are made on the basis of careful comparison of

the short-term and long-term risks of aneurysmal rupture with the risk associated with the intervention, whether it would be surgical clipping or endovascular management. Controversy remains regarding optimum management, and thorough assessments of the risks and benefits of contemporary management options, specific to aneurysm size, location, and many other aneurysm and patient factors, are needed. Endovascular management options continue to improve as micro-catheter technology advances and newer devices and embolic materials are developed. The most commonly used endovascular option is the Guglielmi detachable coil system. This system allows delivery of soft platinum coils into intracranial aneurysms. Overall, clinical trial data showed better recovery data with patients treated endovascularly than treated surgically (3). Findings from several studies also suggested that cerebral aneurysm rupture risk is reduced in patients taking aspirin (4). Recent data support long-term serial screening in individuals with a family history of aneurysmal SAH (5).

Despite the risk factors, including hypertension, cigarette smoking and alcohol use, are more common in men, aneurysmal SAH belongs to a few diseases which the incidence is higher in women than in men (1-3,6,7). Women have a significantly higher risk for *de novo* cerebral aneurysm formation than men in a long-term follow-up study, being female is a significant independent risk factor for aneurysm growth; and women are more likely than men to have multiple cerebral aneurysms (7-9). It has been noted that the incidence was higher in younger men, whereas after the age of 55, the incidence was higher in women (2). Furthermore, earlier age at menopause may be associated with a greater risk of cerebral aneurysm (10). Therefore, a sex-specific hormonal factor may play a role in the pathogenesis of aneurysm formation and rupture.

Sex hormones, especially estrogen, might be protective against cerebral aneurysm rupture (11). Men are at less risk because they do not experience a dramatic estrogen withdrawal as women do. Among women still menstruating, it was suggested the risk for hemorrhage was greatest in the perimenstrual period (11). Clinical trials show hormone replacement therapy (HRT) seems to be associated with a reduced risk for aneurysmal SAH (12,13). Experimental study also demonstrated a sex-specific hormonal factor may play a role in the pathogenesis of aneurysm formation and rupture (14,15). Because it is a relatively common cause of stroke in women under age 65 and because of its high morbidity and mortality, the excess of aneurysmal SAH in women remains a pressing question in stroke research.

The average menopause age in Chinese women has been confirmed to be around 49 years (16,17). A systematic review by de Rooij *et al*. suggested that at younger ages the aneurysmal SAH incidence is higher in men, whereas, after the age of 55, the incidence is higher in women. Recently it was suggested that, while disc degeneration is more common in young men than young women, it is more advanced in elderly women than in elderly men, and women start to show more severe lumbar disc degeneration in their fifties with relatively clear onset time point (18-20). We aimed to see whether such a time point can be detected for aneurysmal SAH, and we hypothesized women's aneurysmal SAH incidence will be higher after middle fifties. The answer to this question may provide some clues about the pathophysiology or even prevention of this deadly condition.

Materials and methods

Aneurysmal SAH cases were collected retrospectively from the archives of eight medical centers in Mainland China, including (I) Nanjing University Medical School Nanjing Drum Tower Hospital, Nanjing (female: 994, male: 684); (II) The Second Hospital of Hebei Medical University (female: 936, male: 561); (III) The Affiliated Hospital of Zunyi Medical University (female: 233, male: 143); (IV) The First Affiliated Hospital of Nanchang University (female: 335, male: 182); (V) North Sichuan Medical College Hospital (female: 359, male: 179); (VI) The First Affiliated Hospital of Xi'an Jiao Tong University (female: 29, male: 19); (VII) The General Hospital of Guangzhou Military Command (female: 50, male: 48); (VIII) Capital Medical University Beijing Friendship Hospital (female: 143, male: 63). All the cases collected were from September 2015 and backward consecutively for a period of time up to 7 years. SAH was initially diagnosed by brain computed tomography, and digital subtraction angiography (DSA) was followed and SAH was confirmed to be due to cerebral aneurysm, and the cases were restricted to first-ever SAH.

Results

In total there were 4,895 cases, with 3,016 females and 1,879 males, and their age distribution is shown in *Figure 1*. Stepwise Chi square test showed there were significantly more male cases of aneurysmal SAH before 37-year-old (*Table S1*). Women started to have a higher incidence of aneurysmal SAH than men after late thirties. In addition,

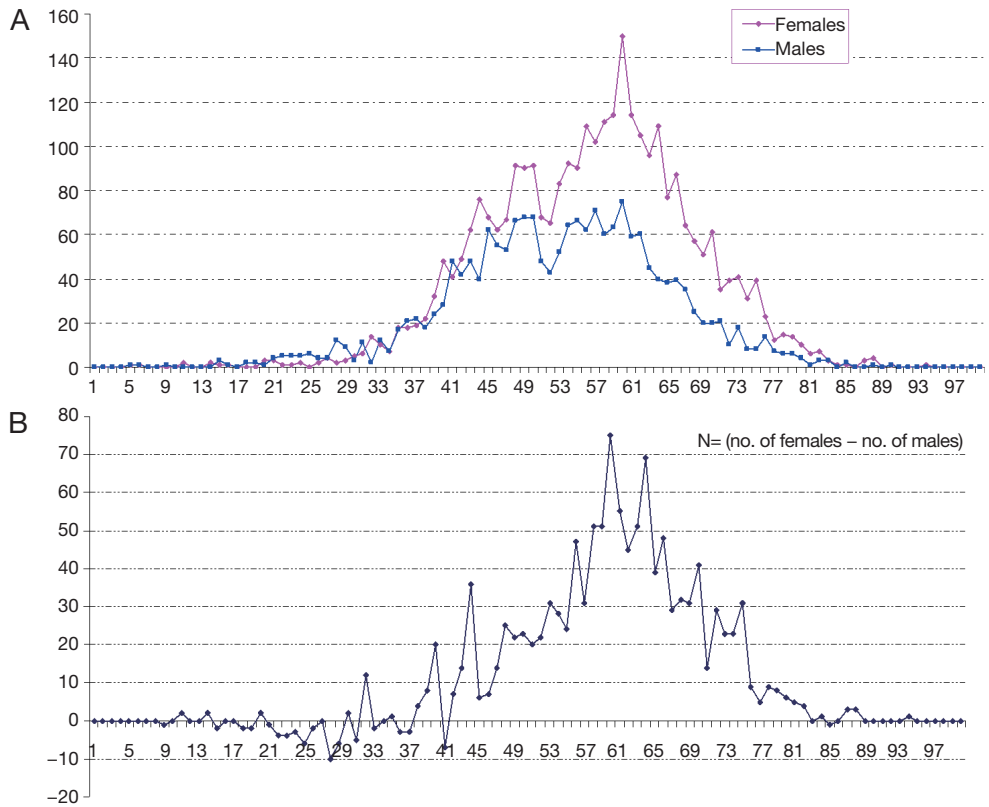

Figure 1 The incidence sporadic aneurysmal subarachnoid hemorrhage (SAH) *vs.* age. (A) The incidence of a total of 4,895 cases of sporadic aneurysmal SAH is plotted against their age; (B) y-axis is the value of incidence of females—incidence of males. X-axis: age in years. The results show women have a higher incidence of aneurysmal SAH than men even prior to menopause, and men might have a higher incidence of aneurysmal SAH than women before late thirties.

the higher incident of aneurysmal SAH in women after their later sixties might be due *by a small portion to* that that women had longer life expectancy than men (20). Our further subgroup analysis according to different centers did not differ from this observation (*Figure 2*, and *Table S2*).

Discussion

Estrogen has a multitude of biological effects that may account for its cardiovascular benefits, including favorable effects on the lipid profile, antioxidant activity, enhanced fibrinolysis (21). Estrogens have been shown to enhance endothelial-dependent relaxation in arterial rings from different vascular beds, including cerebral arteries. Estrogen replacement treatment increases coronary flow and decreases both coronary resistance and peripheral vascular tone (21). Local delivery of 17ß-estradiol during percutaneous transluminal coronary angioplasty improved endothelial function, enhanced re-endothelialization and endothelial NOS expression and decreased neointima formation (21). Estrogen deficiency in postmenopausal women may have a significant impact on the pathophysiology of cerebral aneurysm and SAH. The arteries could undergo postmenopausal connective tissue changes (22). The collagen wasting commonly observed in bone and skin in the postmenopausal period due to decreased estrogen levels could possibly be responsible for the formation of cerebral aneurysms (23-26). Estrogen has been found to improve lipid profiles and thus may reduce the risk for arteriosclerosis, which has been considered a risk factor for aneurysm formation (27,28). Low-dose estrogens are also associated with a reduced blood pressure (29).

Pathology-based therapies for patients harboring unruptured aneurysms may be a reasonable starting point for a disease with otherwise few treatment options. Estrogen might play an important role in vascular and aneurysmal integrity through the control of collagen content and wall thickness (29). Kadasi *et al.* reported that the proportion

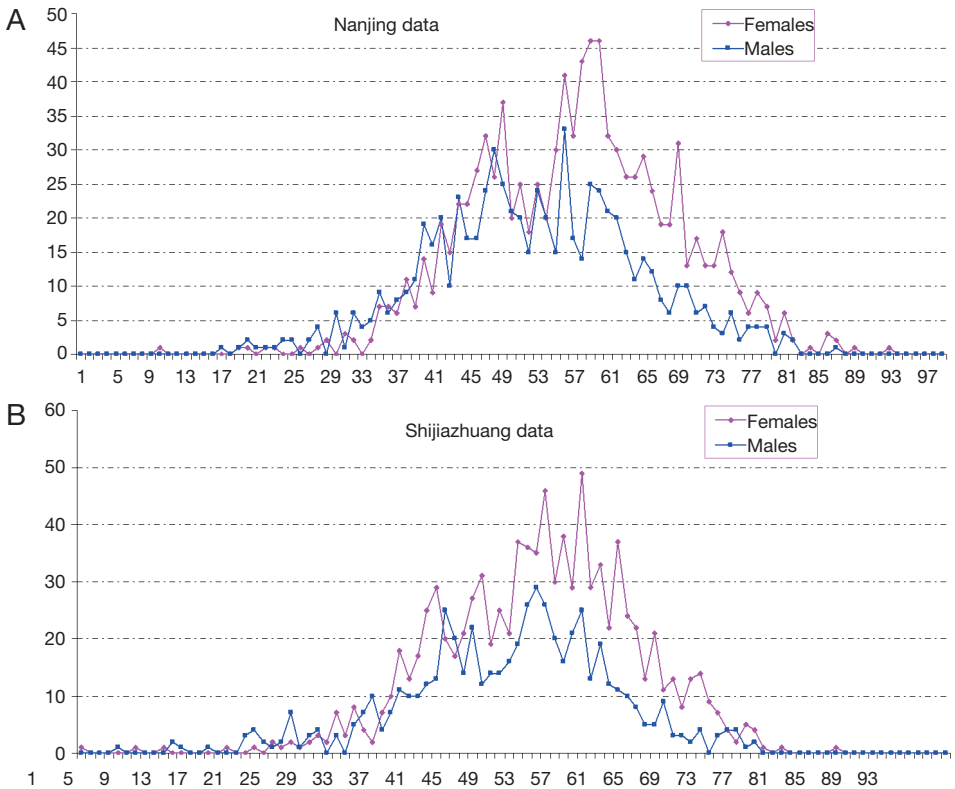

Figure 2 The incidence sporadic aneurysmal subarachnoid hemorrhage (SAH) *vs.* age. (A) The incidence of 1,678 cases of sporadic aneurysmal SAH from Nanjing Drum Tower Hospital is plotted against their age; (B) the incidence of 1,497 cases of sporadic aneurysmal SAH from Hebei Medical University is plotted against their age. X-axis: age in years. The results from each center show similar pattern as demonstrated in *Figure 1*.

of super-thin translucent tissue at the aneurysm dome was significantly greater in women compared with men, suggestive of the susceptibility for rupture (30). The high quality prospective clinical trials by Longstreth *et al*. and Mhurchu *et al*. demonstrated HRT seems to be associated with a reduced risk for aneurysmal SAH (12,13).

While initial clinical studies showed HRT is associated with beneficial cardiovascular effects in postmenopausal women (31,32). The Women's Health Initiative (WHI) hormone trials shows oral estrogens increase the risk of venous thromboembolism among postmenopausal women and increase the risk of breast cancer (33,34). However, the expert views of HRT evolved during the last 10 years since the publication of WHI trials (35). Dose regimen, combination of estrogen with progestins versus estrogen alone, the administration route and duration of treatment such as the choice of repetitive or periodic administration simulating the menstrual cycle are some of the factors that may be involved in the benefit discrepancies. The Estrogen and Thromboembolism Risk (ESTHER) study confirmed that oral estrogens increased venous thromboembolism risk, whereas transdermal estrogens had little or no impact on the development of thrombosis (36). Recent Korean data do not support HRT history for the risk of breast cancer in women (37). It has also been suggested that the presence of gene polymorphisms has also been implicated. If this is the case, estrogen replacement therapy may be useful to prevent cardiovascular disease in a large number of postmenopausal women, but not in a subset of women who are at high risk for cardiovascular and thrombotic complications (21,38). A number of selective estrogen receptor modulators (SERMs) have also been developed. SERMs could be selective in targeting vascular estrogen receptors while having few undesirable effects, such as cardiovascular disease, and breast cancer. It is conceivable that one could design SERMs that would retain the desired effects of estrogen to targeted tissues but devoid of the undesirable effects (39). In one study SERM attenuated the development of experimental aneurysms (40). Phytoestrogens are estrogenic compounds of plant origin classified into different groups with

structural similarities to estrogen that allow them to mimic the effects of estrogen, but less likely have harmful effects (11,35).

There are a number of limitations of our study. This is a retrospective analysis of archived data. There were heterogeneities in different hospital, and the severity of the aneurysmal SAH of individual cases could not be pooled for comparison analysis. On the other hand, the relative large number of cases would likely eliminate potential selection biases.

There is growing interest in the pathogenesis of cerebral aneurysm focused on the development of drug therapies to decrease the incidence of aneurysm growth and rupture, particularly for screening detected female subjects. While our study further suggest that the pathology, etiology, and essential effector of cerebral aneurysm formation and progression are different in men and women and may also differ by age.

Our results disputed our initial hypothesis. Menopause and low estrogen relevant may be relevant in post-menopausal women, but may not be the only dominant factor causing higher incidence of aneurysmal SAH in women. Other possible pathophysiological causes should be further actively explored. Our results may have practical implications for the on-going efforts to development of using estrogen, either alone or in combination with progestogen, to reduce the risk of screening detected cerebral aneurysms from rupture (11-14).

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Chi square P value comparing sex difference

Age	F	M	P value
≤31	29	68	<0.0001
>31	2,976	1,799	<0.0001
≤32	43	70	0.011
>32	2,962	1,797	<0.0001
≤33	53	82	0.013
>33	2,952	1,785	<0.0001
≤34	60	89	0.018
>34	2,945	1,778	<0.0001
≤35	89	118	0.044
>35	2,927	1,761	<0.0001
≤36	107	139	0.041
>36	2,909	1,740	<0.0001
≤37	126	161	0.039
>37	2,890	1,718	<0.0001
≤38	148	179	0.086
>38	2,868	1,700	<0.0001
≤39	180	203	0.24
>39	2,836	1,676	<0.0001
≤40	228	231	0.889
>40	2,788	1,648	<0.0001

Table S2 Aneurysmal subarachnoid hemorrage incidence: age *vs.* sex

Age	Total			Nanjing		Guangzhou		Xi'an		Nanchong		Zunyi		Shijiazhuang		Beijing Friendship		Nanchang	
(yr)	F: no.	M: no.	F-M	F: no.	M: no.	F: no.	M: no.	F: no.	M: no.	F: no.	M: no.	F: no.	M: no.	F: no.	M: no.	F: no.	M: no.	F: no.	M: no.
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0
6	1	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	1	–1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	2	0	2	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	2	0	2	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
15	1	3	–2	0	0	0	0	0	0	0	0	0	0	0	2	0	0	1	1
16	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	2	–2	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0
19	0	2	–2	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0
20	3	1	2	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0
21	3	4	–1	1	2	0	0	0	0	0	1	0	0	1	0	0	0	1	1
22	1	5	–4	0	1	0	1	0	0	0	0	0	0	0	0	0	1	1	2
23	1	5	–4	1	1	0	0	0	1	0	0	0	0	0	3	0	0	0	0
24	2	5	–3	1	1	0	0	0	0	0	0	0	0	1	4	0	0	0	0
25	0	6	–6	0	2	0	0	0	0	0	0	0	2	0	2	0	0	0	0
26	2	4	–2	0	2	0	0	0	0	0	0	0	0	2	1	0	1	0	0
27	4	4	0	1	0	0	0	0	0	1	1	1	0	1	2	0	1	0	0
28	2	12	–10	0	2	0	1	0	0	0	1	0	1	2	7	0	0	0	0
29	3	9	–6	1	4	0	0	0	1	0	0	1	2	1	1	0	0	0	1
30	5	3	2	2	0	1	0	0	0	0	0	0	0	2	3	0	0	0	0
31	6	11	–5	0	6	1	0	0	0	0	1	1	0	3	4	0	0	1	0
32	14	2	12	3	1	1	1	0	0	0	0	3	0	2	0	1	0	4	0
33	10	12	–2	2	6	1	1	0	0	0	1	0	1	7	3	0	0	0	0
34	7	7	0	0	4	0	1	0	0	0	1	1	0	3	0	0	0	3	1
35	18	17	1	2	5	1	1	1	0	0	2	5	4	8	5	1	0	0	0
36	18	21	–3	7	9	0	0	1	0	1	1	2	2	4	7	0	0	3	2
37	19	22	–3	7	6	0	1	0	1	5	1	2	1	2	10	1	0	2	2
38	22	18	4	6	8	1	2	1	0	3	1	3	2	7	4	0	0	1	1
39	32	24	8	11	9	0	1	0	0	1	2	4	2	10	7	1	2	5	1
40	48	28	20	7	11	2	0	0	0	3	2	9	4	18	11	2	0	7	0
41	41	48	–7	14	19	1	0	0	0	8	5	1	2	13	10	2	2	2	10
42	49	42	7	9	16	0	2	0	1	7	1	7	4	17	10	2	3	7	5
43	62	48	14	19	20	1	3	0	0	8	1	1	6	25	12	2	0	6	6
44	76	40	36	15	10	1	0	1	0	8	2	13	9	29	13	2	1	7	5
45	68	62	6	22	23	2	1	0	0	7	5	4	2	20	25	2	2	11	4
46	62	55	7	22	17	3	0	2	0	8	3	6	6	17	20	2	3	2	6
47	67	53	14	27	17	2	2	0	0	8	6	7	8	21	14	1	1	1	5
48	91	66	25	32	24	2	2	0	0	11	5	9	4	27	22	2	1	8	8
49	90	68	22	26	30	1	1	1	0	8	5	9	10	31	12	1	2	13	8
50	91	68	23	37	25	3	3	2	0	10	7	6	11	19	14	0	1	14	7
51	68	48	20	20	21	1	1	0	0	5	3	6	3	25	14	1	1	10	5
52	65	43	22	25	20	1	1	0	1	4	0	8	2	21	16	0	2	6	1
53	83	52	31	18	15	1	8	0	0	6	2	7	2	37	19	2	4	12	2
54	92	64	28	25	24	1	2	1	0	4	5	5	2	36	26	3	3	17	2
55	90	66	24	20	20	0	1	2	1	15	3	2	3	35	29	6	5	10	4
56	109	62	47	30	15	0	1	0	1	7	5	6	5	46	26	3	3	17	6
57	102	71	31	41	33	2	0	1	0	9	6	3	3	30	20	2	3	14	6
58	111	60	51	32	17	0	0	1	0	12	8	8	4	38	16	3	4	17	11
59	114	63	51	43	14	2	0	4	1	14	8	16	4	29	21	1	3	5	12
60	150	75	75	46	25	3	3	2	1	17	10	14	4	49	25	2	1	17	6
61	114	59	55	46	24	5	1	0	1	21	9	1	3	29	13	1	0	11	8
62	105	60	45	32	21	2	1	0	0	20	9	7	3	33	19	2	2	9	5
63	96	45	51	30	20	2	0	2	0	16	5	10	0	22	12	1	2	13	6
64	109	40	69	26	15	1	0	3	1	22	5	7	4	37	11	2	0	11	4
65	77	38	39	26	11	1	0	0	2	14	9	6	3	24	10	1	1	5	2
66	87	39	48	29	14	0	1	0	1	15	5	4	1	22	8	7	1	10	8
67	64	35	29	24	12	1	0	0	1	8	10	7	2	13	5	4	0	7	5
68	57	25	32	19	8	0	0	1	0	5	8	4	2	21	5	2	1	5	1
69	51	20	31	19	6	0	0	0	0	8	1	5	1	11	9	3	1	5	2
70	61	20	41	31	10	0	1	1	0	6	2	2	1	13	3	1	1	7	2
71	35	21	14	13	10	0	0	0	0	8	4	1	2	8	3	1	2	4	0
72	39	10	29	17	6	0	0	0	0	4	0	1	1	13	2	1	0	3	1
73	41	18	23	13	7	1	0	0	1	9	3	2	0	14	4	1	1	1	2
74	31	8	23	13	4	0	0	0	0	1	1	0	1	9	0	1	0	7	2
75	39	8	31	18	3	0	0	0	1	5	0	1	0	7	3	3	0	5	1
76	23	14	9	12	6	0	0	1	0	3	1	1	2	4	4	0	1	2	0
77	12	7	5	9	2	0	0	0	0	0	1	1	0	2	4	0	0	0	0
78	15	6	9	6	4	0	0	0	0	1	0	1	0	5	1	1	0	1	1
79	14	6	8	9	4	0	0	0	0	0	0	1	0	4	2	0	0	0	0
80	10	4	6	7	4	0	0	1	0	1	0	0	0	1	0	0	0	0	0
81	6	1	5	2	0	0	0	0	0	1	0	0	0	0	0	2	0	1	1
82	7	3	4	6	3	0	0	0	0	0	0	0	0	1	0	0	0	0	0
83	3	3	0	2	2	0	0	0	1	0	0	0	0	0	0	0	0	1	0
84	1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
85	1	2	–1	1	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
87	3	0	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
88	4	1	3	2	1	0	0	0	0	0	0	0	0	1	0	1	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
90	1	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
94	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
sum	3,016	1,879		994	684	50	48	29	19	359	179	233	143	936	561	80	63	335	182
sum	4,895																		