

**TABLE 2. Odds ratios (95% confidence interval) for undergoing hospitalization and median values (interquartile range) of medical expenditure per month for respective hospitalization in the year after baseline in the 183 862 male and 130 760 female participants, grouped according to hypertension status at baseline, based on data from the medical insurance system in Japan**

	Optimal blood pressure	Normal-to-high normal blood pressure	Grade 1 untreated hypertension	Grade 2 untreated hypertension	Grade 3 untreated hypertension	Well controlled hypertension on treatment	Poorly controlled hypertension on treatment
<b>Men aged 40–54 years</b>	<i>(n</i> = 38 320)	<i>(n</i> = 41 063)	<i>(n</i> = 12 599)	<i>(n</i> = 3594)	<i>(n</i> = 1136)	<i>(n</i> = 4473)	<i>(n</i> = 4112)
No hospitalization							
Cases ( <i>n</i> )	36 685	39 148	11 929	3383	1049	4102	3757
Medical expenditure (euros)	13 (0–43)	14 (0–48)	15 (0–58)	18 (0–78)	27 (0–95)	144 (95–206)	132 (85–192)
Hospitalization							
Cases ( <i>n</i> )	1635	1915	670	211	87	371	355
Rate (%)	4.27	4.66	5.32	5.87	7.66	8.29	8.63
Odds ratio (vs. optimal)	1.00 Reference	1.02 (0.96–1.10)	1.10 (1.00–1.21)	1.20 (1.03–1.40)	1.59 (1.27–2.00)	1.48 (1.31–1.68)	1.51 (1.33–1.71)
Odds ratio (vs. well controlled)	0.68 (0.60–0.77)	0.69 (0.61–0.78)	0.74 (0.65–0.85)	0.81 (0.68–0.97)	1.08 (0.84–1.38)	1.00 Reference	1.02 (0.88–1.19)
Medical expenditure (euros)	373 (176–730)	371 (196–765)	411 (203–854)	444 (251–1245)	623 (338–1460)	472 (275–895)	478 (248–913)
In hospitalization (euros)	229 (90–537)	239 (100–544)	274 (108–632)	302 (136–1028)	446 (179–1166)	214 (76–537)	195 (63–579)
Cases of ≥7 cumulative days/year ( <i>n</i> )	869	1051	384	135	61	215	194
Rate (%)	2.27	2.56	3.05	3.76	5.37	4.81	4.72
Odds ratio (vs. optimal)	1.00 Reference	1.08 (0.98–1.18)	1.22 (1.07–1.38)	1.49 (1.23–1.80)	2.17 (1.66–2.85)	1.61 (1.37–1.90)	1.56 (1.32–1.85)
Odds ratio (vs. well controlled)	0.62 (0.53–0.73)	0.67 (0.57–0.78)	0.75 (0.63–0.90)	0.92 (0.74–1.16)	1.35 (1.00–1.81)	1.00 Reference	0.97 (0.79–1.18)
Medical expenditure (euros)	661 (395–1233)	644 (393–1251)	698 (418–1199)	840 (435–1784)	1095 (545–2313)	726 (467–1292)	803 (470–1677)
In hospitalization (euros)	476 (275–976)	477 (283–1042)	527 (297–1020)	645 (299–1583)	971 (385–1679)	446 (254–991)	466 (246–1245)
Cases of ≥14 cumulative days/year ( <i>n</i> )	490	584	213	87	41	113	114
Rate (%)	1.28	1.42	1.69	2.42	3.61	2.53	2.77
Odds ratio (vs. optimal)	1.00 Reference	1.08 (0.95–1.22)	1.22 (1.03–1.44)	1.73 (1.37–2.19)	2.64 (1.90–3.67)	1.55 (1.24–1.93)	1.68 (1.35–2.10)
Odds ratio (vs. well controlled)	0.65 (0.52–0.81)	0.70 (0.56–0.86)	0.79 (0.62–1.00)	1.12 (0.84–1.50)	1.71 (1.18–2.47)	1.00 Reference	1.09 (0.83–1.42)
Medical expenditure (euros)	1009 (612–1769)	1024 (624–1783)	1000 (627–1759)	1288 (732–2513)	1460 (992–2524)	1211 (729–2168)	1241 (659–2517)
In hospitalization (euros)	813 (453–1413)	813 (476–1513)	836 (472–1437)	1161 (581–2116)	1166 (830–2361)	866 (459–1812)	878 (424–1749)
<b>Men aged 55–69 years</b>	<i>(n</i> = 16 873)	<i>(n</i> = 26 726)	<i>(n</i> = 12 050)	<i>(n</i> = 3677)	<i>(n</i> = 997)	<i>(n</i> = 9356)	<i>(n</i> = 8886)
No hospitalization							
Cases ( <i>n</i> )	15 594	24 534	11 024	3320	908	8338	7971
Medical expenditure (euros)	24 (0–84)	24 (0–85)	27 (0–93)	26 (0–100)	37 (0–118)	151 (92–225)	141 (85–210)
Hospitalization							
Cases ( <i>n</i> )	1279	2192	1026	357	89	1018	915
Rate (%)	7.58	8.20	8.51	9.71	8.93	10.88	10.30
Odds ratio (vs. optimal)	1.00 Reference	1.05 (0.98–1.13)	1.06 (0.97–1.16)	1.24 (1.09–1.40)	1.12 (0.89–1.41)	1.27 (1.16–1.39)	1.18 (1.08–1.30)
Odds ratio (vs. well controlled)	0.79 (0.72–0.86)	0.83 (0.76–0.90)	0.83 (0.76–0.91)	0.97 (0.85–1.11)	0.88 (0.70–1.11)	1.00 Reference	0.93 (0.85–1.02)
Medical expenditure (euros)	472 (243–1071)	482 (246–1062)	512 (256–1179)	504 (277–1128)	596 (314–1102)	590 (356–1125)	589 (338–1202)
In hospitalization (euros)	292 (120–747)	302 (118–814)	335 (136–911)	324 (129–872)	385 (156–874)	280 (117–729)	297 (112–844)
Cases of ≥7 cumulative days/year ( <i>n</i> )	783	1298	643	226	57	573	555
Rate (%)	4.64	4.86	5.34	6.15	5.72	6.12	6.25
Odds ratio (vs. optimal)	1.00 Reference	1.02 (0.93–1.12)	1.09 (0.98–1.22)	1.27 (1.09–1.49)	1.16 (0.88–1.54)	1.16 (1.04–1.31)	1.17 (1.04–1.32)
Odds ratio (vs. well controlled)	0.86 (0.77–0.97)	0.88 (0.79–0.97)	0.94 (0.83–1.06)	1.10 (0.93–1.29)	1.00 (0.75–1.33)	1.00 Reference	1.01 (0.89–1.14)
Medical expenditure (euros)	783 (448–1517)	833 (480–1589)	887 (489–1776)	822 (442–1507)	795 (583–1787)	934 (593–1780)	859 (562–1807)
In hospitalization (euros)	544 (309–1187)	595 (331–1283)	652 (333–1447)	610 (307–1277)	667 (365–1577)	586 (320–1356)	585 (311–1392)
Cases of ≥14 cumulative days/year ( <i>n</i> )	449	796	401	141	39	350	342
Rate (%)	2.66	2.98	3.33	3.83	3.91	3.74	3.85
Odds ratio (vs. optimal)	1.00 Reference	1.10 (0.97–1.24)	1.19 (1.04–1.37)	1.38 (1.14–1.68)	1.38 (0.98–1.93)	1.24 (1.07–1.44)	1.26 (1.09–1.47)
Odds ratio (vs. well controlled)	0.81 (0.70–0.94)	0.89 (0.78–1.01)	0.96 (0.83–1.12)	1.12 (0.91–1.37)	1.11 (0.79–1.56)	1.00 Reference	1.02 (0.88–1.19)
Medical expenditure (euros)	1274 (754–2075)	1290 (744–2134)	1325 (761–2163)	1189 (716–1908)	1154 (687–2104)	1338 (859–2276)	1319 (817–2444)
In hospitalization (euros)	1017 (544–1679)	1009 (563–1747)	1058 (583–1841)	940 (571–1606)	908 (510–1884)	972 (533–1847)	1021 (562–1939)

(Continued)

TABLE 2 (Continued)

	Optimal blood pressure	Normal-to-high normal blood pressure	Grade 1 untreated hypertension	Grade 2 untreated hypertension	Grade 3 untreated hypertension	Well controlled hypertension on treatment	Poorly controlled hypertension on treatment
Women aged 40–54 years	(n = 39 090)	(n = 21 635)	(n = 5082)	(n = 1275)	(n = 371)	(n = 2089)	(n = 1530)
No hospitalization							
Cases (n)	37 410	20 776	4866	1215	353	1962	1428
Medical expenditure (euros)	26 (7–66)	25 (6–69)	28 (5–82)	32 (4–93)	50 (9–123)	144 (93–214)	136 (93–197)
Hospitalization							
Cases (n)	1680	859	216	60	18	127	102
Rate (%)	4.30	3.97	4.25	4.71	4.85	6.08	6.67
Odds ratio (vs. optimal)	1.00 Reference	0.91 (0.84–0.99)	0.96 (0.83–1.12)	1.07 (0.82–1.39)	1.09 (0.68–1.76)	1.33 (1.10–1.62)	1.45 (1.17–1.80)
Odds ratio (vs. well controlled)	0.75 (0.62–0.91)	0.69 (0.56–0.84)	0.72 (0.58–0.91)	0.80 (0.58–1.10)	0.82 (0.49–1.37)	1.00 Reference	1.09 (0.83–1.43)
Medical expenditure (euros)	453 (200–804)	476 (223–879)	461 (239–943)	591 (355–925)	583 (394–1584)	621 (380–1122)	642 (356–1106)
In hospitalization (euros)	293 (95–564)	322 (117–618)	315 (108–653)	351 (166–655)	422 (237–1489)	316 (132–764)	321 (138–661)
Cases of ≥7 cumulative days/year (n)	966	504	136	38	12	76	68
Rate (%)	2.47	2.33	2.68	2.98	3.23	3.64	4.44
Odds ratio (vs. optimal)	1.00 Reference	0.91 (0.82–1.02)	1.01 (0.84–1.22)	1.12 (0.80–1.56)	1.20 (0.67–2.14)	1.30 (1.01–1.66)	1.55 (1.19–2.03)
Odds ratio (vs. well controlled)	0.77 (0.60–0.99)	0.71 (0.55–0.91)	0.78 (0.59–1.04)	0.87 (0.58–1.29)	0.92 (0.50–1.72)	1.00 Reference	1.20 (0.86–1.68)
Medical expenditure (euros)	696 (485–1136)	726 (476–1268)	756 (419–1171)	720 (527–1226)	1210 (535–2210)	971 (610–1517)	863 (592–1581)
In hospitalization (euros)	515 (335–779)	542 (339–954)	559 (308–898)	501 (292–982)	857 (305–2000)	586 (342–980)	545 (289–1365)
Cases of ≥14 cumulative days/year (n)	455	247	68	19	9	48	37
Rate (%)	1.16	1.14	1.34	1.49	2.43	2.30	2.42
Odds ratio (vs. optimal)	1.00 Reference	0.91 (0.77–1.06)	0.98 (0.75–1.27)	1.07 (0.67–1.71)	1.70 (0.87–3.35)	1.50 (1.09–2.07)	1.49 (1.04–2.15)
Odds ratio (vs. well controlled)	0.67 (0.48–0.92)	0.60 (0.44–0.83)	0.65 (0.44–0.95)	0.71 (0.41–1.22)	1.13 (0.55–2.35)	1.00 Reference	1.00 (0.64–1.54)
Medical expenditure (euros)	1077 (688–1810)	1199 (714–2101)	1081 (716–2019)	1221 (645–1992)	1447 (581–2311)	1291 (777–2061)	1396 (922–2312)
In hospitalization (euros)	773 (518–1437)	926 (542–1723)	827 (560–1662)	949 (472–1740)	1402 (407–2162)	865 (493–1723)	1142 (601–3291)
Women aged 55–69 years	(n = 18 733)	(n = 20 481)	(n = 7135)	(n = 1704)	(n = 450)	(n = 6190)	(n = 4995)
No hospitalization							
Cases (n)	17 639	19 324	6702	1619	428	5707	4638
Medical expenditure (euros)	42 (10–107)	45 (10–113)	45 (9–118)	55 (10–132)	51 (5–130)	154 (100–232)	154 (99–226)
Hospitalization							
Cases (n)	1094	1157	433	85	22	483	357
Rate (%)	5.84	5.65	6.07	4.99	4.89	7.80	7.15
Odds ratio (vs. optimal)	1.00 Reference	0.90 (0.83–0.98)	0.93 (0.82–1.04)	0.74 (0.59–0.93)	0.71 (0.46–1.11)	1.11 (0.99–1.25)	0.97 (0.85–1.11)
Odds ratio (vs. well controlled)	0.90 (0.80–1.01)	0.81 (0.72–0.91)	0.83 (0.72–0.95)	0.67 (0.52–0.85)	0.64 (0.41–1.00)	1.00 Reference	0.88 (0.76–1.01)
Medical expenditure (euros)	489 (265–919)	508 (276–1021)	580 (287–1212)	674 (317–1327)	542 (282–908)	597 (345–1177)	663 (370–1399)
In hospitalization (euros)	287 (118–619)	323 (120–687)	389 (139–866)	488 (155–945)	444 (104–724)	293 (105–795)	328 (118–823)
Cases of ≥7 cumulative days/year (n)	623	719	278	60	14	319	225
Rate (%)	3.33	3.51	3.90	3.52	3.11	5.15	4.50
Odds ratio (vs. optimal)	1.00 Reference	0.99 (0.88–1.10)	1.04 (0.90–1.21)	0.92 (0.70–1.21)	0.79 (0.46–1.36)	1.27 (1.10–1.47)	1.06 (0.90–1.25)
Odds ratio (vs. well controlled)	0.79 (0.68–0.91)	0.78 (0.68–0.89)	0.82 (0.69–0.97)	0.73 (0.55–0.96)	0.62 (0.36–1.07)	1.00 Reference	0.83 (0.70–0.99)
Medical expenditure (euros)	785 (498–1379)	779 (476–1477)	873 (531–1654)	927 (559–1708)	777 (548–1070)	864 (520–1535)	933 (579–1838)
In hospitalization (euros)	542 (313–1029)	530 (316–1125)	599 (382–1323)	642 (408–1183)	637 (481–927)	572 (276–1105)	582 (314–1454)
Cases of ≥14 cumulative days/year (n)	358	405	178	43	11	170	129
Rate (%)	1.91	1.98	2.49	2.52	2.44	2.75	2.58
Odds ratio (vs. optimal)	1.00 Reference	0.95 (0.82–1.10)	1.12 (0.93–1.35)	1.10 (0.80–1.52)	1.00 (0.54–1.85)	1.11 (0.91–1.35)	0.98 (0.79–1.22)
Odds ratio (vs. well controlled)	0.90 (0.74–1.10)	0.85 (0.71–1.03)	1.01 (0.81–1.25)	0.99 (0.70–1.40)	0.90 (0.48–1.68)	1.00 Reference	0.89 (0.70–1.12)
Medical expenditure (euros)	1107 (727–1826)	1283 (750–1990)	1290 (740–1995)	1190 (750–2144)	883 (748–1232)	1336 (914–2112)	1595 (961–2368)
In hospitalization (euros)	827 (512–1496)	945 (529–1635)	997 (544–1672)	915 (581–1648)	678 (612–1025)	963 (635–1740)	1285 (552–91921)

Data are presented for the male and female population stratified according to age at baseline. Optimal blood pressure was defined as an SBP < 120 mmHg and a DBP < 80 mmHg; normal-to-high normal blood pressure as an SBP 120–139 mmHg and/or DBP 80–89 mmHg; grade 1 untreated hypertension as an SBP 140–159 mmHg and/or DBP 90–99 mmHg; grade 2 untreated hypertension as an SBP 160–179 mmHg and/or DBP 100–109 mmHg; grade 3 untreated hypertension as an SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg; well controlled hypertension on treatment as an SBP < 140 mmHg and DBP < 90 mmHg on antihypertensive medication; and poorly controlled hypertension on treatment as an SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg on medication. Odds ratios were calculated using a logistic regression model with multivariate adjustment for age, BMI, smoking habits, serum low-density lipoprotein cholesterol, medication for hypercholesterolemia, log-transformed fasting plasma glucose, and medication for diabetes. One euro = 95.91 Japanese yen, 0.79 pounds sterling, and 1.22 US dollars at the foreign exchange rates on 1 August 2012.

**TABLE 3. Odds ratios (95% confidence interval) for falling into the top 1% group of medical expenditure in the year after baseline in the 183 862 male and 130 760 female participants, grouped according to hypertension status at baseline**

	Optimal blood pressure	Normal-to-high normal blood pressure	Grade 1 untreated hypertension	Grade 2 untreated hypertension	Grade 3 untreated hypertension	Well controlled hypertension on treatment	Poorly controlled hypertension on treatment
Men aged 40–54 years	(n = 38 320)	(n = 41 063)	(n = 12 599)	(n = 3594)	(n = 1136)	(n = 4473)	(n = 4112)
Cases (n)	191	220	80	41	19	52	56
Rate (%)	0.50	0.54	0.63	1.14	1.67	1.16	1.36
Odds ratio (vs. optimal)	1.00 Reference	1.03 (0.85–1.26)	1.15 (0.88–1.50)	2.07 (1.46–2.92)	3.12 (1.93–5.06)	1.63 (1.18–2.27)	1.92 (1.39–2.65)
Odds ratio (vs. well controlled)	0.61 (0.44–0.85)	0.63 (0.46–0.87)	0.70 (0.49–1.01)	1.27 (0.83–1.93)	1.91 (1.12–3.28)	1.00 Reference	1.17 (0.80–1.72)
Men aged 55–69 years	(n = 16 873)	(n = 26 726)	(n = 12 050)	(n = 3677)	(n = 997)	(n = 9356)	(n = 8886)
Cases (n)	203	351	187	56	18	183	181
Rate (%)	1.20	1.31	1.55	1.52	1.81	1.96	2.04
Odds ratio (vs. optimal)	1.00 Reference	1.09 (0.91–1.30)	1.25 (1.02–1.54)	1.24 (0.92–1.67)	1.44 (0.88–2.35)	1.46 (1.18–1.80)	1.53 (1.23–1.89)
Odds ratio (vs. well controlled)	0.69 (0.56–0.85)	0.74 (0.62–0.90)	0.86 (0.70–1.06)	0.85 (0.62–1.15)	0.99 (0.60–1.61)	1.00 Reference	1.04 (0.85–1.29)
Women aged 40–54 years	(n = 39 090)	(n = 21 635)	(n = 5082)	(n = 1275)	(n = 371)	(n = 2089)	(n = 1530)
Cases (n)	247	151	37	10	6	31	22
Rate (%)	0.63	0.70	0.73	0.78	1.62	1.48	1.44
Odds ratio (vs. optimal)	1.00 Reference	1.04 (0.84–1.28)	1.01 (0.71–1.45)	1.09 (0.57–2.08)	2.26 (0.99–5.18)	1.77 (1.19–2.65)	1.67 (1.05–2.67)
Odds ratio (vs. well controlled)	0.56 (0.38–0.84)	0.59 (0.39–0.88)	0.57 (0.35–0.93)	0.62 (0.30–1.27)	1.28 (0.53–3.11)	1.00 Reference	0.94 (0.54–1.64)
Women aged 55–69 years	(n = 18 733)	(n = 20 481)	(n = 7135)	(n = 1704)	(n = 450)	(n = 6190)	(n = 4995)
Cases (n)	198	250	108	23	2	117	105
Rate (%)	1.06	1.22	1.51	1.35	0.44	1.89	2.10
Odds ratio (vs. optimal)	1.00 Reference	1.08 (0.90–1.31)	1.28 (1.00–1.63)	1.11 (0.72–1.73)	0.35 (0.09–1.41)	1.46 (1.15–1.86)	1.57 (1.21–2.02)
Odds ratio (vs. well controlled)	0.69 (0.54–0.87)	0.74 (0.59–0.93)	0.88 (0.67–1.15)	0.76 (0.48–1.20)	0.24 (0.06–0.97)	1.00 Reference	1.07 (0.82–1.40)

Data are presented for the male and female population stratified according to age at baseline. Optimal blood pressure was defined as an SBP <120 mmHg and a DBP <80 mmHg; normal-to-high normal blood pressure as an SBP 120–139 mmHg and/or DBP 80–89 mmHg; grade 1 untreated hypertension as an SBP 140–159 mmHg and/or DBP 90–99 mmHg; grade 2 untreated hypertension as an SBP 160–179 mmHg and/or DBP 100–109 mmHg; grade 3 untreated hypertension as an SBP ≥180 mmHg and/or DBP ≥110 mmHg; well controlled hypertension on treatment as an SBP <140 mmHg and DBP <90 mmHg on antihypertensive medication; and poorly controlled hypertension on treatment as an SBP ≥140 mmHg and/or DBP ≥90 mmHg on medication. Male and female participants who fell into the sex-specific top 1% medical expenditure group each incurred ≥1571 euros/month and ≥1249 euros/month, respectively. Odds ratios were calculated using a logistic regression model with multivariate adjustment for age, BMI, smoking habits, serum low-density lipoprotein cholesterol, medication for hypercholesterolemia, log-transformed fasting plasma glucose, and medication for diabetes. One euro = 95.91 Japanese yen, 0.79 pounds sterling, and 1.22 US dollars, at the foreign exchange rates on 1 August 2012.

regardless of hypertension status. As a consequence, hospitalized cases attributable to overall hypertension, including normal-to-high normal blood pressure, untreated hypertension and treated hypertension incurred 6.9–7.2 and 2.8–3.8% of the total medical expenditure in the male and female study population solely as a consequence of hospitalization. Compared with well controlled hypertension on treatment or grade 1-to-2 untreated hypertension, grade 3 untreated hypertension also had a higher risk of incurring extremely high medical expenditure, such as falling into the top 1% group costing at least 1571 euros/month for men and at least 1249 euros/month for women.

A previous 10-year prospective cohort study in Japan reported that individuals with untreated hypertension had a higher risk of hospitalization and death, and incurred on average higher medical expenditure, compared with normotensive individuals [12]. In contrast to this long-term follow-up study, our 1-year follow-up period may have been suitable for comparing hospitalization risk and medical expenditure for normal blood pressure, untreated hypertension, and treated hypertension, but was unable to identify the reason for hospitalization. This suitability of our study is based on the fact that it is impossible to assume that baseline conditions (i.e., blood pressure levels and treatment status) remain unchanged throughout a long follow-up period. Our data also demonstrated that blood pressure was a predictor of short-term surges in medical

expenditure. Although hypertension has an effect on medical expenditure in contrast to optimal blood pressure, good control of hypertension lowers the risk of surges in medical expenditure because of hospitalization of hypertensive individuals. A notable, relevant study carried out in Canada [17] suggested that better adherence to antihypertensive medication correlated with a lower risk of cardiovascular events, hospitalization, and lower total costs in newly treated hypertensive individuals. On the contrary, a study in the United States [16] suggested that hospitalization risk decreased with increased adherence to medication, although there was no significant difference in total costs across adherence levels. Our results on hospitalization risk are consistent with the findings of these previous studies, although our results do not indicate whether treatment of hypertension offsets long-term medical costs. However, our results indicate that hypertensive individuals on medication incur relatively low medical expenditure as long as they remain out of hospital for treatment of hypertension alone.

In Japan, cardiovascular, cerebrovascular, and renal disease incurs 17.8% of the total medical costs in the population aged 45–64 years through any medical cause, whereas the inpatient costs for treatment of these serious vascular diseases account for 9.2% of the total costs [18]. Our estimates suggest that overall hypertension contributes significantly to inpatient medical expenditure for treatment

**TABLE 4.** Mean values  $\pm$  standard deviation of inpatient medical expenditure per month and percentages of inpatient medical expenditure attributable to hypertension relative to total medical expenditure in the year after baseline in the 183 862 male and 130 760 female participants, grouped according to hypertension status at baseline, based on the medical insurance system in Japan

	Optimal blood pressure	Normal-to-high normal blood pressure	Grade 1 untreated hypertension	Grade 2 untreated hypertension	Grade 3 untreated hypertension	Well controlled hypertension on treatment	Poorly controlled hypertension on treatment
Men aged 40–54 years	(n = 38 320)	(n = 41 063)	(n = 12 599)	(n = 3594)	(n = 1136)	(n = 4473)	(n = 4112)
Inpatient expenditure (euros)	22 $\pm$ 236	26 $\pm$ 278	31 $\pm$ 259	50 $\pm$ 377	80 $\pm$ 496	46 $\pm$ 315	49 $\pm$ 334
Percentage of inpatient expenditure attributable to that category relative to total expenditure (%)		1.8	1.2	1.1	0.7	1.2	1.2
Men aged 55–69 years	(n = 16 873)	(n = 26 726)	(n = 12 050)	(n = 3677)	(n = 997)	(n = 9356)	(n = 8886)
Inpatient expenditure (euros)	50 $\pm$ 332	57 $\pm$ 407	64 $\pm$ 370	69 $\pm$ 384	65 $\pm$ 329	72 $\pm$ 409	77 $\pm$ 447
Percentage of inpatient expenditure attributable to that category relative to total expenditure (%)		1.5	1.3	0.5	0.1	1.6	1.9
Women aged 40–54 years	(n = 39 090)	(n = 21 635)	(n = 5082)	(n = 1275)	(n = 371)	(n = 2089)	(n = 1530)
Inpatient expenditure (euros)	21 $\pm$ 195	23 $\pm$ 239	26 $\pm$ 251	38 $\pm$ 399	40 $\pm$ 247	36 $\pm$ 253	55 $\pm$ 427
Percentage of inpatient expenditure attributable to that category relative to total expenditure (%)		0.7	0.4	0.3	0.1	0.5	0.8
Women aged 55–69 years	(n = 18 733)	(n = 20 481)	(n = 7135)	(n = 1704)	(n = 450)	(n = 6190)	(n = 4995)
Inpatient expenditure (euros)	34 $\pm$ 286	35 $\pm$ 273	45 $\pm$ 335	42 $\pm$ 370	31 $\pm$ 244	53 $\pm$ 351	55 $\pm$ 402
Percentage of inpatient expenditure attributable to that category relative to total expenditure (%)		0.2	0.9	0.2	0	1.3	1.2

Data are presented for the male and female population stratified according to age at baseline. Optimal blood pressure was defined as an SBP <120 mmHg and a DBP <80 mmHg; normal-to-high normal blood pressure as an SBP 120–139 mmHg and/or DBP 80–89 mmHg; grade 1 untreated hypertension as an SBP 140–159 mmHg and/or DBP 90–99 mmHg; grade 2 untreated hypertension as an SBP 160–179 mmHg and/or DBP 100–109 mmHg; grade 3 untreated hypertension as an SBP  $\geq$  180 mmHg and/or DBP  $\geq$  110 mmHg; well controlled hypertension on treatment as an SBP <140 mmHg and/or DBP <90 mmHg on antihypertensive medication; and poorly controlled hypertension on treatment as an SBP  $\geq$  140 mmHg and/or DBP  $\geq$  90 mmHg on medication. Total medical expenditure was 9191 780 euros for men aged 40–54 years, 12 890 866 euros for men aged 55–69 years, 6441 909 euros for women aged 40–54 years, and 8807 015 euros for women aged 55–69 years. One euro = 95.91 Japanese yen, 0.79 pounds sterling, and 1.22 US dollars, at the foreign exchange rates on 1 August 2012.

of these serous vascular diseases, at least in men. Furthermore, as reported by a national survey in Japan, inpatient medical expenditure attributable to overall hypertension may be broadly comparable to medical expenditure for treatment of hypertension itself [18]. It should be noted that most inpatient medical expenditure attributable to overall hypertension may come from various cases of hypertension other than well controlled hypertension on treatment. In particular, from a population perspective based on the Rose's theory that 'a large number of people exposed to a small risk may generate many more cases than a small number exposed to high risk' [31], it is important not to ignore normal-to-high normal blood pressure and grade 1 untreated hypertension, which are usually nonurgent cases for antihypertensive medication [19]. This will ensure comprehensive prevention of serious clinical outcomes and increased medical expenditure.

Our results in all men and middle-aged women were in accordance with evidence of a positive, graded relationship between blood pressure and risk of cardiovascular, cerebrovascular, and renal disease in individuals not taking antihypertensive medication at baseline [1–5], and also that the efficacy of appropriate antihypertensive treatment lowers the risk of serious vascular diseases in a hypertensive population [20–22,32]. However, we observed a less apparent relationship of increased risk of hospitalization with the severity of untreated hypertension in

presenile women, compared with the other sex and age-groups. Although it is difficult to explain these discrepant results, the following facts may account for these differences. In general, the positive relationship between blood pressure and morbidity and mortality risk is less apparent in older than in younger individuals [1,33]. In addition, it is possible the participants may have been misclassified because of a single random blood pressure measurement, especially in women who showed greater differences between screening and home blood pressure measurements (i.e. white-coat hypertension) than men [34,35]. Our results may therefore have been underestimated, especially in women. Furthermore, the small number of untreated severe hypertensive participants and the short-term follow-up period may have resulted in failure to identify the true relationship in women who have a lower morbidity and mortality rate than men [33,36].

The current study had several limitations. First, we could not identify particular diseases that directly increased the risk of undergoing long-term hospitalization or particular treatments that incurred inpatient medical expenditure in hypertensive participants. Second, information on the details of untreated hypertension (e.g. whether hypertension had been recently or previously identified) and the details of treated hypertension (e.g. hypertensive grade before starting medication, prescriptions, and usual control

status) was not available. Of the hypertensive participants on treatment, some may not have taken their antihypertensive medication the morning of the examination day, partially because of screening for gastric cancer at the same time, and may therefore have provided unreliable information on their usual blood pressure on medication. Consequently, they may have been misclassified as poorly controlled, despite their usual blood pressure being well controlled on treatment. Even though the majority of poorly controlled hypertensive participants on treatment were true cases at the baseline survey, medication added after the survey may have led to well controlled hypertension. This possible misclassification may have led to an underestimation of the true effect of poorly controlled hypertension on hospitalization risk. Our results regarding treated hypertension should also be interpreted with caution, as the Japan Arteriosclerosis Longitudinal Study [37] found no stepwise increase in stroke risk across blood pressure levels in hypertensive individuals on medication, and that the risk of stroke was significantly higher even at optimal levels of blood pressure in the medication group compared with optimal blood pressure in the group not taking medication. Third, we could not identify the reason why 0.48% ( $n=1522$ ) of the participants dropped out mid-study with a median (interquartile range) follow-up period of 7 (3–10) months. The rates of dropout in the five medication-off categories from optimal blood pressure to grade 3 untreated hypertension were 0.37, 0.48, 0.54, 0.46, and 0.24%, whereas the corresponding rates in the well controlled and poorly controlled hypertension on treatment categories were 0.77 and 0.76%, respectively. Further studies are therefore needed to refine the methodological study limitations mentioned above. Finally, this economic topic is dependent on the costs of medical services, which differ across countries. Therefore, our results cannot necessarily be extrapolated to other countries.

In conclusion, our study suggests that hospitalization status is an important determinant when considering medical expenditure associated with hypertension. From an individual viewpoint, severe untreated hypertension is more likely to incur extremely high medical expenditure as a result of hospitalization, compared with well controlled hypertension on treatment or mild untreated hypertension. Using antihypertensive medication to prevent serious clinical outcomes which incur extremely high medical costs may be a key strategy for reducing the disease and economic burden associated with hypertension.

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## Conflicts of interest

There are no conflicts of interest.

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## Reviewer's Summary Evaluation

### Reviewer 1

**Strengths:** The study investigates the effect of hypertension on hospitalization risk and medical expenditures according to the treatment status in a Japanese population of 314 622 subjects classified into seven blood pressure categories. In both men and women grade 3 untreated hypertension led to a more frequent hospitalization and higher medical

expenditures compared with treated hypertension and grade 1–2 untreated hypertension. These data confirm that in grade 3 hypertension medical expenditures of treated subjects are significantly lower than those of untreated subjects.

**Weakness:** The global cardiovascular risk of the subject has not been reported in detail. The causes directly increasing the risk of long term hospitalization in hypertensive subjects were not identified, and this is a consistent limitation.

