

Disproportional increase of pulmonary embolism in young females in Germany: trends from 2005 to 2014

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Published online: 20 February 2017
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Abstract We analysed the number of pulmonary embolism (PE) in young females aged 10–39 years in the period from 2005 to 2014 in Germany to see any trends that possibly may reflect some influences of newer oral contraceptives. Detailed lists of all hospitalized cases with the principal diagnosis PE coded as I26 in the years 2005–2014 were provided by the Federal Statistical Office. In males, the absolute number of all hospitalized cases with the principal diagnosis PE increased from 16,066 in 2005 to 25,364 in 2014 (rate +57.8%) and in females from 21,548 to 29,433 (rate +36.5%). The annual differences in PE between males and females decreased from 5482 to 4069 (–26%) in this period. In the age group of 10–39 years the absolute number of all hospitalized male cases increased from 1023 in 2005 to 1276 in 2014 (+24.7%) and in females from 1341 to 1949 (rate +45.3%). Thus in contrast to the overall trend the annual difference in PE rose gradually by 112% (from 318 to 673) from 2005 to 2014. Our ecologic nationwide analysis of hospitalization rates for PE shows that the annual differences between males and females cases hospitalized with the principal diagnosis PE in general decreased, but increased in the age group of 10–39 years in the last decade.

Keywords Pulmonary embolism · Hospitalised patients · DRG statistics · Gender

Introduction

In 2010, we described gender-specific differences in young people aged 10–39 years hospitalised for pulmonary embolism (PE) as principal diagnosis based on the German DRG statistics [1, 2]. The presented data showed that there is a sharp increase in hospitalization with PE in females beginning with 12–13 years compared to males. Up to the ages of 32–33 years females were hospitalized more often with PE than males; even so, the absolute numbers are small for both sexes.

In Germany we do not have population based data regarding the global effect of oral contraceptives (OC) on hospitalization rates of females with PE. In hospitalized females with PE the use of (OC) is not documented, but we think that any effect of newer OC on the incidence of PE in young females must affect hospitalization rates. Thus we analyzed overall hospitalization rates associated with PE as principal diagnosis in the decade from 2005 to 2014 and compared it with hospitalization rates associated with PE in young people aged 10–39 years.

Patients and methods

The national statistics (DRG statistics) published by the Federal Statistical Office includes data from all hospitals in Germany that use the DRG system which covers more than 99% (see [2]). These hospitals are legally obliged to provide extensive data on hospital treatment, including demographic data, diagnoses, co-morbidities, complications, and

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procedures to the “Institute for the Hospital Remuneration System” (InEK), which uses the data for a yearly adaptation of the German DRG system and transmits them to the Federal Statistical Office. From 2005 to 2014 all diagnoses were coded with the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), which was adapted for Germany by the German Institute for Medical Documentation and Information (DIMDI) as ICD-10 German Modification (ICD-10-GM) in the corresponding annual version. PE was coded as with (I26.0) and without (I26.9) acute cor pulmonale (ACP).

Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Statistics

Detailed lists of all cases with PEs documented as principal diagnosis and separately of cases aged 10–39 years were provided by the Federal Statistical Office. Cases were divided into those with (I26.0) and those without (I26.9) ACP. In addition detailed lists of all diagnoses coded as additional diagnosis were provided. Calculations were

done using Microsoft® Excel 2003 and Microsoft® Access 2003.

Results

Figure 1 shows the absolute number of cases with PE in the age groups 10–39 years representative only for the years 2005 and 2014. The results from the omitted years went in the same direction. There is a sharp increase in hospitalization with PE in females beginning with 12–13 years compared to males and the reunion of the curves in the fourth decade of life. The largest difference between males and females is seen in the ages 14–19 years.

Absolute number of all cases hospitalized with the principal diagnosis PE increased from 37,614 in 2005 to 54,797 in 2014 (+46%). Absolute number of all cases aged 10–39 years hospitalized with the principal diagnosis PE increased from 2364 in 2005, which represent only 6.3% of cases in 2005. It increased to 3225 in 2014 (+36%).

The overall increase in males was higher with 58% (from 16,066 in 2005 to 25,364 in 2014) than in females with 37% only (from 21,548 to 29,433, Table 1). In the age group of 10–39 years the increase was higher in females than in males. In males the figures increased by 25% (from 1023 in 2005 to 1276 in 2014) and in females by 45% (from

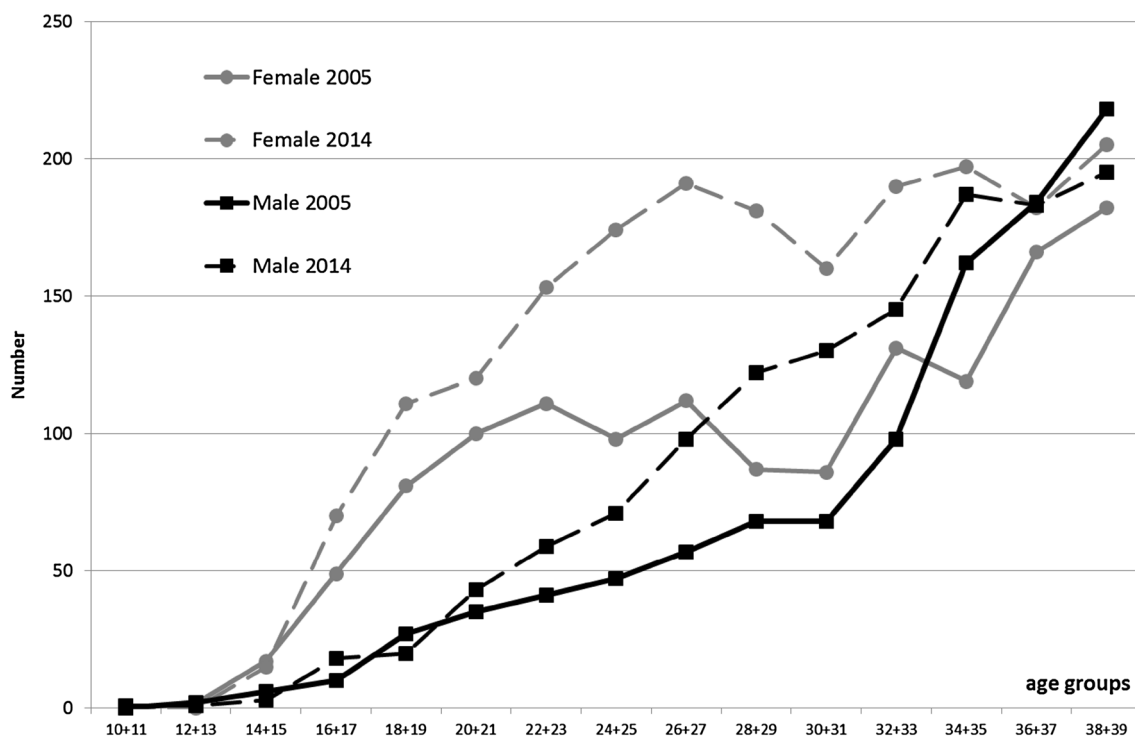


Fig. 1 Absolute numbers of PEs (ICD codes: I26.0 and 26.9) documented as principal diagnosis in the years 2005 and 2014 separated for males and females listed in 2 year age groups. For better visibility

we skip the years in between but the results from the omitted years went in the same direction

Table 1 Listed is the number of all male and female cases hospitalized for PE documented as principal diagnosis for the years 2005 to 2014 and that of all male and female cases aged 10–39 years

Year	All			Cases aged 10–39 years		
	Males	Females	Delta	Males	Females	Delta
2005	16,066	21,548	5482	1023	1341	318
2006	17,623 (+10%)	22,925 (+6%)	5302 (−3%)	1132 (+11%)	1511 (+13%)	379 (+19%)
2007	18,304 (+14%)	23,639 (+10%)	5335 (−3%)	1086 (+6%)	1549 (+16%)	463 (+46%)
2008	19,882 (+24%)	25,474 (+18%)	5592 (+2%)	1173 (+15%)	1659 (+24%)	486 (+53%)
2009	20,999 (+31%)	26,514 (+23%)	5515 (+1%)	1195 (+17%)	1732 (+29%)	537 (+69%)
2010	22,868 (+42%)	27,687 (+28%)	4819 (−12%)	1236 (+21%)	1842 (+37%)	606 (+91%)
2011	22,848 (+42%)	27,628 (+28%)	4780 (−13%)	1232 (+20%)	1787 (+33%)	505 (+59%)
2012	24,367 (+52%)	29,057 (+35%)	4690 (−14%)	1230 (+20%)	1832 (+37%)	602 (+89%)
2013	25,484 (+59%)	29,808 (+38%)	4324 (−21%)	1268 (+24%)	1990 (+48%)	721 (+127%)
2014	25,364 (+58%)	29,433 (+37%)	4069 (−26%)	1276 (+25%)	1949 (+45%)	673 (+112%)

Delta is the difference between males and female cases in each year. The changes compared to the year 2005 are given in percent in parenthesis

1341 in 2005 to 1949 in 2014). Thus, in the 10 years period the annual difference in absolute numbers of all hospitalized cases decreased by 26% (from 5482 to 4069), whereas it increased by 112% (from 318 in 2005 to 673 in 2014) cases aged 10–39 years.

The increase of all PEs in females and males as well as the increase of PEs in cases aged 10–39 years is primarily driven by an increase in PE without ACP (Table 2). Thus

the ratio of PE without and PE with ACP increased in both genders from 2.61 to 3.56 in males and from 2.44 to 3.31 in females.

Documented additional diagnoses are listed in Table 3 and do not show striking changes in comorbidity. Obesity is more frequent in females compared to males, but rates decreased from 2005 to 2014 in both genders and in the total group and the younger ages. Morbus Crohn

Table 2 Hospitalized male and female cases with PE separated for acute cor pulmonale (with or without)

Year	Males			Females		
	With	Without	Ratio	With	Without	Ratio
2005	6146	9920	2:61	9071	12477	2:44
	283 (4.6%)	740 (7.5%)		390 (4.3%)	951 (7.6%)	
2006	6409	11,214	2:93	9048	13,877	2:47
	288 (4.5%)	844 (7.5%)		436 (4.8%)	1075 (7.7%)	
2007	6363	11,941	3:04	8986	14,653	2:84
	269 (4.2%)	817 (6.8%)		403 (4.5%)	1146 (7.8%)	
2008	6616	13,266	3:14	370	16,104	2:80
	281 (4.2%)	882 (6.6%)		437 (4.7%)	1222 (7.6%)	
2009	6738	14,261	2:81	9502	17,012	2:62
	314 (4.7%)	881 (6.2%)		479 (5.0%)	1253 (7.4%)	
2010	7019	15,849	3:54	9501	18,186	2:73
	272 (3.9%)	962 (6.1%)		494 (5.2%)	1348 (7.4%)	
2011	6593	16,255	3:56	9061	18,567	3:02
	270 (4.1%)	962 (5.9%)		444 (4.9%)	1343 (7.2%)	
2012	6958	17,409	3:20	9156	19,901	3:28
	293 (4.2%)	937 (5.4%)		428 (4.7%)	1404 (7.1%)	
2013	7266	18,218	3:68	9297	20,511	3:04
	270 (3.7%)	993 (5.5%)		493 (5.3%)	1497 (7.3%)	
2014	6904	18,460	3:56	9043	20,390	3:31
	280 (4.1%)	996 (5.4%)		452 (5.0%)	1497 (7.3%)	

Given are the absolute numbers of cases, the absolute number of cases aged 10–39 years and in parenthesis its ratio of all in percent. In addition ratio of PEs with and without acute cor pulmonale calculated for the cases aged 10–39 years is listed

Table 3 List of documented comorbidities in all and in 10–39 years old hospitalized male and female cases with PE

All		Males		Females	
Codes	Diseases	2005	2014	2005	2014
		n = 16,066	n = 25,364	n = 21,548	n = 29,433
C00-D90	Neoplasm	6981 (43.5)	10,425 (41.1)	8396 (38.9)	11,928 (40.5)
E00-E90	Endocrine diseases or diseases of nutrition and metabolism	9129 (56.8)	19,248 (75.9)	16,618 (77.0)	29,737 (101.0)
	E66: obesity	1529 (9.5)	1981 (7.8)	3011 (14.0)	3027 (10.3)
F00-F99	Psychological and behavioural disorders	1875 (11.7)	4244 (16.7)	4283 (19.8)	6338 (21.5)
	F10: associated with alcohol	422 (2.6)	501 (2.0)	101 (0.5)	114 (0.4)
	F11: associated with opioids	32 (0.2)	54 (0.2)	16 (0.1)	20 (0.1)
	F32: depression	292 (1.8)	653 (2.6)	906 (4.2)	1468 (5.0)
I00-I99	Diseases of the vascular system	29,547 (183.9)	49,626 (195.7)	40,922 (189.6)	59,214 (201.2)
	I80: venous thrombosis	7499 (46.7)	12,498 (49.3)	8873 (41.1)	12,984 (44.1)
	I46: cardiac arrest	466 (2.9)	965 (3.8)	571 (2.6)	1046 (3.6)
J00-J99	Diseases of respiratory system	10406 (64.8)	22,014 (86.8)	11,630 (53.9)	23,723 (80.6)
	J15–18: pneumonia	3802 (23.7)	7451 (29.4)	3987 (18.5)	6574 (22.3)
K00-K93	Diseases of gastrointestinal system	5584 (34.8)	13,266 (52.3)	7409 (34.3)	14,173 (48.2)
	K50-K51: M. Crohn, Colitis	122 (0.8)	185 (0.7)	109 (0.5)	182 (0.6)
N00-N99	Diseases of urogenital systems	4528 (28.2)	9617 (37.9)	6809 (31.5)	13,069 (44.4)
O00-O99	Pregnancy, delivery and childbed	–	–	59 (0.3)	49 (0.2)
S00-T98	Injuries, toxicities	1046 (6.5)	2206 (8.7)	2100 (9.7)	3059 (10.4)
10–39 years old		n = 1023	n = 1276	n = 1341	n = 1949
C00-D90	Neoplasm	304 (29.7)	320 (25.1)	537 (40.0)	585 (30.0)
E00-E90	Endocrine diseases or diseases of the nutrition and metabolism	310 (30.3)	442 (34.6)	536 (40.0)	843 (43.3)
	E66: obesity	128 (12.5)	137 (10.7)	248 (18.5)	248 (12.7)
F00-F99	Psychological and behavioural disorders	263 (25.7)	300 (23.5)	271 (20.2)	359 (18.4)
	F10: associated with alcohol	36 (3.5)	40 (3.1)	4 (0.3)	6 (0.3)
	F11: associated with opioids	23 (2.2)	17 (1.3)	19 (1.4)	9 (0.5)
	F32: depression	14 (1.4)	36 (2.8)	25 (1.9)	50 (2.6)
I00-I99	Diseases of the vascular system	936 (91.5)	1161 (91.09)	1030 (76.8)	1406 (72.1)
	I80: venous thrombosis	517 (50.5)	650 (50.9)	551 (41.1)	749 (38.4)
	I46: cardiac arrest	19 (1.9)	29 (2.3)	1 (0.1)	9 (0.5)
J00-J99	Diseases of respiratory system	607 (59.3)	975 (76.4)	638 (47.6)	1298 (66.6)
	J15–18: pneumonia	354 (34.6)	539 (42.2)	323 (24.2)	661 (33.9)
K00-K93	Diseases of gastrointestinal system	222 (21.7)	361 (28.3)	191 (14.2)	340 (17.4)
	K50-K51: M. Crohn, Colitis	21 (2.1)	19 (1.5)	18 (1.3)	23 (1.2)
N00-N99	Diseases of urogenital systems	68 (6.6)	86 (6.7)	115 (8.6)	176 (9.0)
O00-O99	Pregnancy, delivery and childbed	–	–	55 (4.1)	49 (2.5)
S00-T98	Injuries, toxicities	56 (5.5)	79 (6.2)	101 (7.5)	140 (7.2)

Some comorbidities are grouped according to their codes, some are listed specifically. Given are the absolute number of cases and in parenthesis its ratio of all in percent

or colitis was documented only in few patients in rates in 2014 are lower than in 2005. The same is true for opioids which might play a specific role in younger addicts and for the codes covering pregnancy, delivery and childbed.

Discussion

The presented data taken from the German DRG statistics shows that in the last decade the annual differences between

males and females cases hospitalized with the principal diagnosis PE in general decreased, but increased in the age group of 10–39 years.

There are increasing numbers of cases hospitalized with PE in both genders in Germany since 2005. This increase is driven by cases without ACP. This finding is in agreement with the literature. The ESC guidelines on the diagnosis and management of acute PE reported a growing evidence suggesting over-diagnosis of PE [3]. Data from the United States show an 80% rise in the apparent incidence of PE after the introduction of CT, without a significant impact on mortality [4, 5].

The disproportional increase in hospitalized cases with PE in females aged 10–39 years in the last decade has not been reported before. It is in contrast to the general trend. The difference in absolute numbers of female and male cases became smaller. In contrast, the number of female cases aged 10–39 years increased more than the male cases and the annual difference became greater. We do not know what causes this increase in hospitalization for PE in young females from 2005 to 2014. PE in younger people is a multicausal disease with changing influence of the risk factors in the different age groups. Pregnancy and oral contraception but also trauma, obesity, venous compression syndromes, inflammatory bowel disease and intravenous drug abuse have been reported to be typical risk factors in such a young population [1, 6, 7]. A specific increase of one of these risk factors in females aged 10–39 years could not be demonstrated. Thus a general impact of new OC in this young group of females has to be discussed. Most literature reports relative risks that range from a 2 to fivefold risk with pregnancy and combined hormonal contraception [8–11]. A nested case-control and cohort study from UK included 186 newly diagnosed, idiopathic cases of VTE aged 15–44 years matched with 681 controls. The odds ratio for VTE comparing use of OC containing drospirenone with use of those containing levonorgestrel was 2.3 (95% confidence interval 1.6–3.2) [12–14]. A German community-based, case-control study recruited 680 VTE cases from the primary care sector estimated the crude odds ratio (OR) for VTE associated with current use of newer OCs in comparison to women who had never used a OCs before the index date was 1.9 (1.5–2.5), the adjusted OR was 2.3 (1.7–3.0) [10]. All these data describe a higher VTE Risk but do not really describe the size of the problem. Accepting that in Germany 13,500,000 females are aged 10–39 years and 50% of them use oral contraceptives the absolute difference between males and females of 673 cases hospitalized with PE in 2014 is small. Because of the changes to newer OC only the increase of 355 cases might be attributed to the introduction of newer OCs. This small number goes along with the effect that the gender specific difference is highest in the ages of 13–25 years whereas the absolute number

of cases with PE is low in this ages. Today this is not the typical age of pregnancy in Germany any more but for first use of OC. In contrast, most of the literature discussing the problem of OC related VTEs include females up to 45 [2, 14] or 49 years [15]. As first users have a higher risk than ongoing users future analysis of newer OC associated VTE risk should focus on first users aged 13–25 years.

Strength and limitations

A major strength of this study is the large data set which includes virtually all German hospitals and the observation period of 10 years. This allows a unique view at the current clinical practice. Moreover, to the best of our knowledge, there is currently no other publication addressing this topic from a population based viewpoint in Germany.

There are factors that limit our results. First, our ecologic study design did not allow control for confounding including life style. Second, the primary diagnosis is on the physician's own authority and strongly affects the reimbursement in the German DRG system. Third, it should be pointed out that the analysis is based on cases and not on individual patients. As a consequence, a patient may be included several times in the statistics if he had recurrent events at different times within 1 year. Forth, comparison of the presented data with other studies has to consider differences in study populations as well as the uncertainty about the diagnosis PE.

In conclusion, our ecologic nationwide analysis of hospitalization rates for PE shows that the annual differences between males and females cases hospitalized with the principal diagnosis PE in general decreased, but increased in the age group of 10–39 years in the last decade. The possible impact of oral contraception for this increase has to be further elucidated.

Acknowledgements We thank Referat VIII A 1 from the Federal Statistical Office for extracting and providing the data from the DRG-Statistik.

Funding No fundings received.

Compliance with ethical standards

Conflict of interest F. Santosa, Ch. Moerchel, Ch. Berg declares that they have no conflict of interest. K. Kröger has received a speaker honorarium from Bayer, Sanofi, Bristol Myers Squibb.

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