Article

A long-term trend of drug-induced deaths in European countries

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Received 20 December 2016; *Accepted 16 January 2017*; *Published 1 December 2017*
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Abstract
In present study, data of drug-induced deaths in 29 European countries were used to analyze the profile and trend of drug-induced deaths recorded for total population, males and females in order to provide some basic information on adverse effects and misuse of drugs. The results showed that Germany (28501 deaths) and United Kindom (22537 deaths) have the greatest accumalted number (1995~2014) of drug-induced deaths, followed by Italy (14134 deaths) and Spain (11133 deaths). Germany (23%) and United Kingdom (18%) held the highest percentage of drug-induced deaths in Europe, followed by Italy (12%), Spain (9%), Sweden (4%), and Norway (4%), etc. For males, United Kindom (24%) and Germany (20%) held the highest percentage, followed by Poland (8%), Italy (6%), etc. Similarly, Germany (25%) and United Kingdom (18%) are the highest in death percentage of males, followed by Italy (13%), etc. Not less than 1 death/yr, the European countries with the highest linear growth of drug-induced deaths for total population (p<0.05) are Turkey (33.2 deaths/yr) and Sweden (21.6 deaths/yr), followed by Ireland (8.9 deaths/yr), Estonia (7.3 deaths/yr), Finland (6.5 deaths/yr), Lithuania (2.6 deaths/yr), and Romania (2.3 deaths/yr). Not less than 1 death/yr, the European countries with the highest linear decline of drug-induced deaths for total population (p<0.05) are Italy (-53.9 deaths/yr) and Germany (-42.1 deaths/yr), followed by Spain (-21.6 deaths/yr), Portugal (-9.8 deaths/yr), Czech Republic (-2.9 deaths/yr), and Hungry (-1.5 deaths/yr). In average, the number of drug-induced deaths for both total population and males in Europe declined at the annual rate of 2 deaths, and that for females grew at the annual rate of 0.1 death. Generally the continuous growth of drug-induced deaths was mostly attributed to the growth of drug uses, the deteriorated medical service, or the promotion of diagnostic levels, etc. However, the continuous decline of drug-induced deaths was mostly attributed to the enhancement of medical service and the improvement of drug uses. More attention may be focused on females for proper drug uses. Both proper drug uses and improved drug design in reducing adverse effects are needed in the future.

Keywords drug; toxicity; adverse effects; abuse; deaths; Europe.

Network Pharmacology
ISSN 2415-1084
URL: http://www.iaees.org/publications/journals/np/online-version.asp
RSS: http://www.iaees.org/publications/journals/np/rss.xml
E-mail: networkpharmacology@iaees.org
Editor-in-Chief: WenJun Zhang
Publisher: International Academy of Ecology and Environmental Sciences

1 Introduction

According to the data analysis of the years 2010~2016, Prescrire Rédaction (2017) presented a list of 91 drugs with adverse effects, of which 82 are sold in France. The list covers a wide range of drugs, including drugs to

treat cancers, diabetes, arthritis, allergies, Alzheimer's disease, nausea and vomiting. For example, some drugs for the treatment of colds, such as pseudo-ephedrine (pseudoéphédrine) will expose the patient to the risk of serious cardiovascular disease or death (e.g., hypertension, stroke, arrhythmia, etc.). In addition, drugs used to relieve sore throat or cough, such as Muxol or Bisolvon, are only a placebo, and not proven effective, which may cause allergic reactions and severe skin allergies, and sometimes are fatal. Obviously, adverse effects and abuse of drugs are becoming one of the major problems in drug uses. In present study, the data of drug-induced deaths in European countries were used to analyze the profile and trend of drug-induced deaths recorded for total population, males and females, in order to provide some basic information on adverse effects and misuse of drugs.

2 Materials and Methods

Data of drug-induced deaths in 29 European countries were collected from EUROSTAT (European Commission, 2017; http://ec.europa.eu/health/home_en). Three indices, number of drug-induced deaths recorded for total population, males and females were analyzed. Data range was generally from 1995 to 2014, but data for some countries and years were absent.

Time series of above three populations were assumed to be a linear function of year. I used linear regression (Zhang et al., 2006; Zhang, et al., 2007; Zhang and Zhang, 2007; Zhang, 2008) to fit the trends for each of the countries and indices (Table 2): $x = a + b\ t$, where t is year, x is drug-induced deaths at t, and b is the annual growth rate of drug-induced deaths. Linear regressions were statistically tested with F-statistic, based on r^2 for the regression.

Simple statistics, e.g., percentage, total, etc., were also used to analyze the data.

3 Results and Analysis

3.1 Accumulated number of drug-induced deaths

As indicated in Table 1, Germany (28501 deaths) and United Kindom (22537 deaths) have the greatest accumalted number (1995~2014) of drug-induced deaths, followed by Italy (14134 deaths) and Spain (11133 deaths).

3.2 Percentage of accumulated number of drug-induced deaths

The accumulated numbers of drug-induced deaths during 1995~2014 are indicated in Fig. 1 a-c. Germany (23%) and United Kingdom (18%) held the highest percentage of drug-induced deaths in Europe (Fig. 1a), followed by Italy (12%), Spain (9%), Sweden (4%), and Norway (4%), etc. For males, United Kindom (24%) and Germany (20%) held the highest percentage, followed by Poland (8%), Italy (6%), etc (Fig. 1 b). Similarly, Germany (25%) and United Kingdom (18%) are the highest in dealth percentage of males, followed by Italy (13%), etc (Fig. 1 c).

3.3 Linear trends of drug-induced deaths recorded for three populations

3.3.1 Total population

Not less than 1 death/yr, the European countries with the highest linear growth of drug-induced deaths for total population (p<0.05) are Turkey (33.2 deaths/yr) and Sweden (21.6 deaths/yr), followed by Ireland (8.9 deaths/yr), Estonia (7.3 deaths/yr), Finland (6.5 deaths/yr), Lithuania (2.6 deaths/yr), and Romania (2.3 deaths/yr) (Table 2).

Not less than 1 death/yr, the European countries with the highest linear decline of drug-induced deaths for total population (p<0.05) are Italy (-53.9 deaths/yr) and Germany (-42.1 deaths/yr), followed by Spain (-21.6 deaths/yr), Portugal (-9.8 deaths/yr), Czech Republic (-2.9 deaths/yr), and Hungry (-1.5 deaths/yr).

3.3.2 Females

Not less than 1 death/yr, the European country with the highest linear growth of drug-induced deaths for females (p<0.05) is United Kingdom (17.9 deaths/yr), followed by Sweden (8.2 deaths/yr), France (2.5 deaths/yr), Ireland (1.9 deaths/yr) and Finland (1.1 deaths/yr) (Table 2). Not less than 1 death/yr, the European countries with the significant linear decline (p<0.05) include Germany (-6.8 deaths/yr), Italy (-4.5 deaths/yr), and Spain (-2.6 deaths/yr).

3.3.3 Males

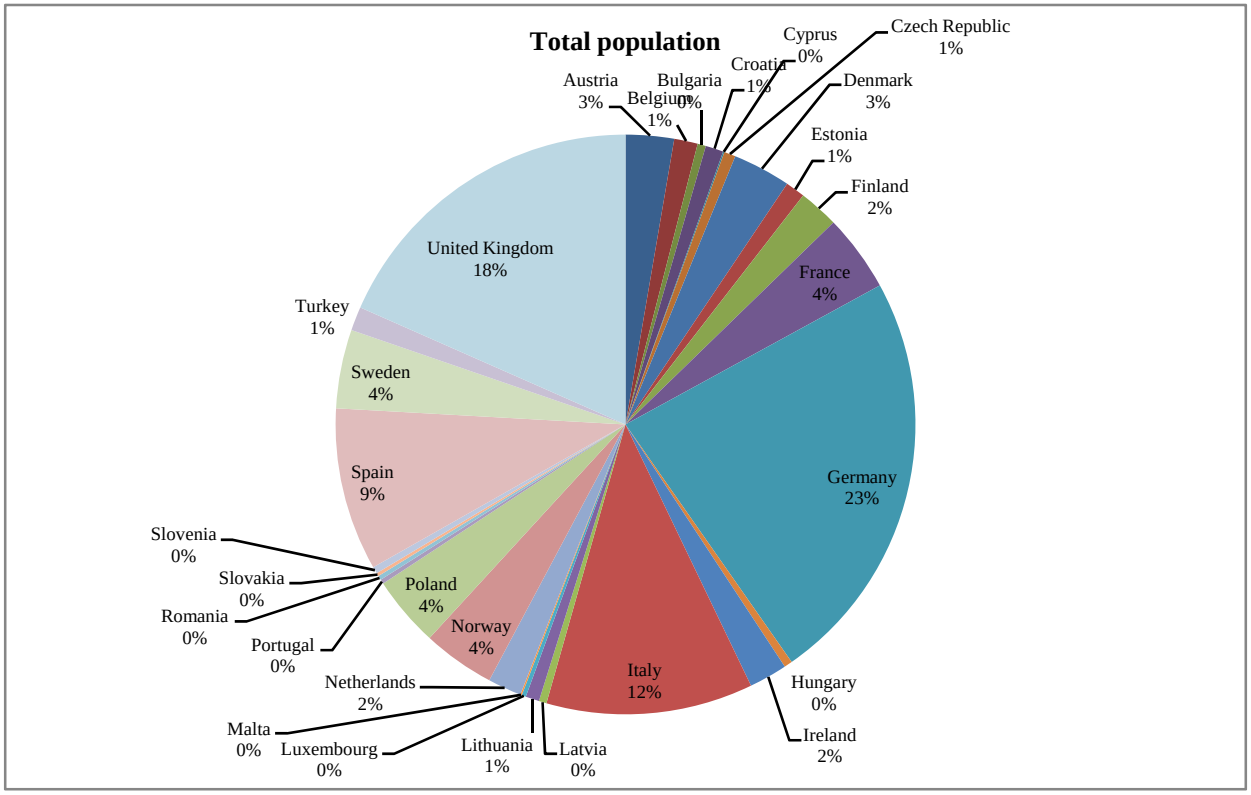
Not less than 1 death/yr, the European country with the highest linear growth of drug-induced deaths for males (p<0.05) is Turkey (31.8 deaths/yr), followed by Sweden (14.8 deaths/yr), Ireland (7.0 deaths/yr), Estonoa (6.4 deaths/yr), Finland (5.4 deaths/yr), Lithuania (2.5 deaths/yr), Romania (1.8 deaths/yr), and Denmark (1.5 deaths/yr). Not less than 1 death/yr, the European countries with the significant linear decline (p<0.05) include Italy (-49.4 deaths/yr), Germany (-35.9 deaths/yr), Spain (-26.2 deaths/yr), Portugal (-8.9 deaths/yr), Hungary (-1.0 deaths/yr).

In average, the number of drug-induced deaths for both total population and males in Europe declined at the annual rate of 2 deaths, and that for females grew at the annual rate of 0.1 deaths, but the trends were not statistically significant.

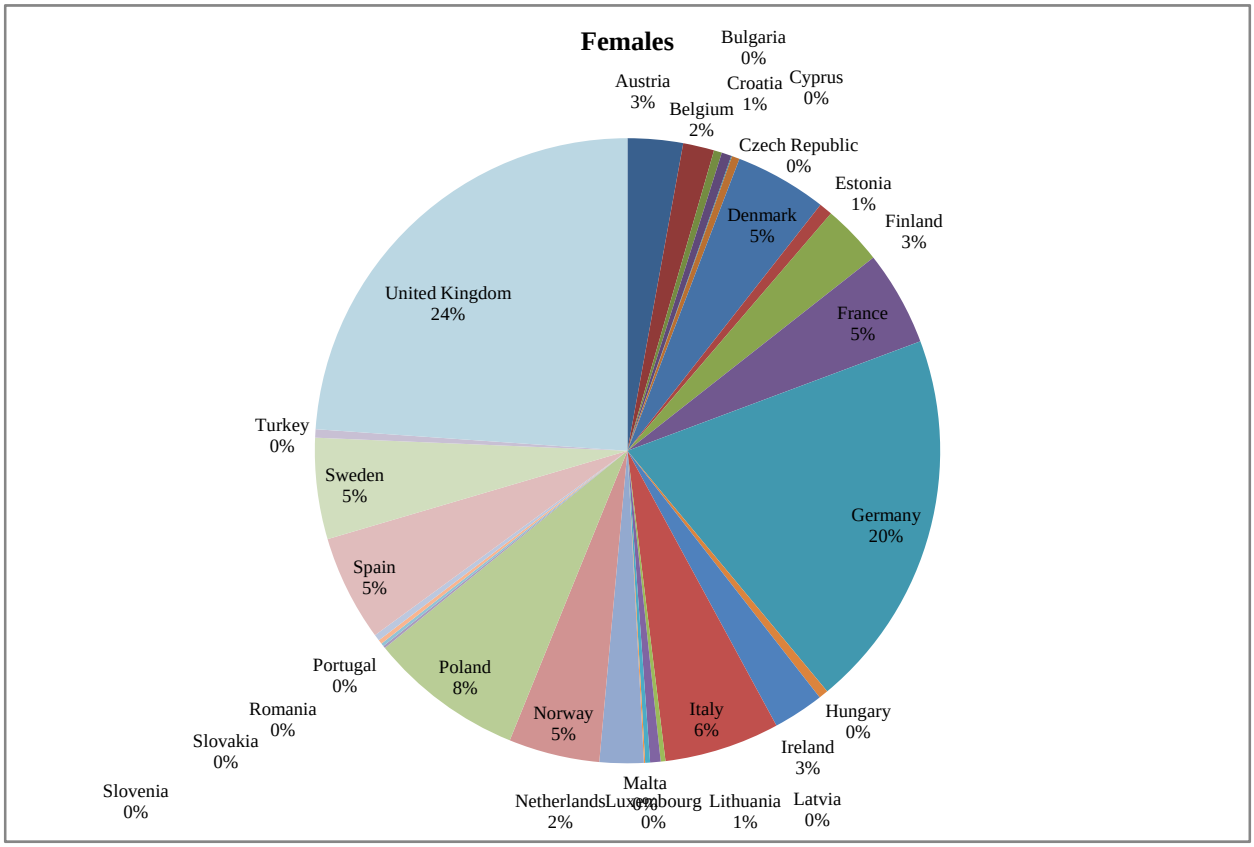
Table 1 Accumulated number of drug-induced deaths in European countries during 1995~2014.

Females		Males		Total	
United Kingdom	5328	Germany	23743	Germany	28501
Germany	4384	United Kingdom	17209	United Kingdom	22537
Poland	1783	Italy	12804	Italy	14134
Italy	1330	Spain	7124	Spain	11133
Spain	1221	France	4185	Sweden	5390
Sweden	1165	Sweden	4084	France	5280
France	1095	Norway	3748	Norway	4939
Denmark	1061	Poland	3043	Poland	4826
Norway	1048	Denmark	2834	Denmark	3961
Finland	696	Austria	2671	Austria	3306
Austria	636	Finland	2034	Finland	2730
Ireland	587	Ireland	2026	Ireland	2613
Netherlands	508	Netherlands	1795	Netherlands	2303
Belgium	359	Turkey	1538	Turkey	1635
Estonia	154	Belgium	1247	Belgium	1606
Lithuania	120	Estonia	1184	Estonia	1338
Croatia	114	Croatia	986	Croatia	1216
Hungary	109	Lithuania	806	Lithuania	926
Turkey	97	Bulgaria	481	Czech Republic	780
Bulgaria	92	Czech Republic	467	Bulgaria	573
Czech Republic	89	Hungary	452	Hungary	561
Slovenia	74	Latvia	432	Latvia	528
Luxembourg	56	Slovenia	393	Slovenia	467
Latvia	55	Portugal	272	Portugal	305
Slovakia	46	Romania	256	Romania	293
Romania	37	Luxembourg	230	Luxembourg	286
Portugal	27	Slovakia	180	Slovakia	226
Malta	14	Malta	95	Malta	109
Cyprus	9	Cyprus	87	Cyprus	96

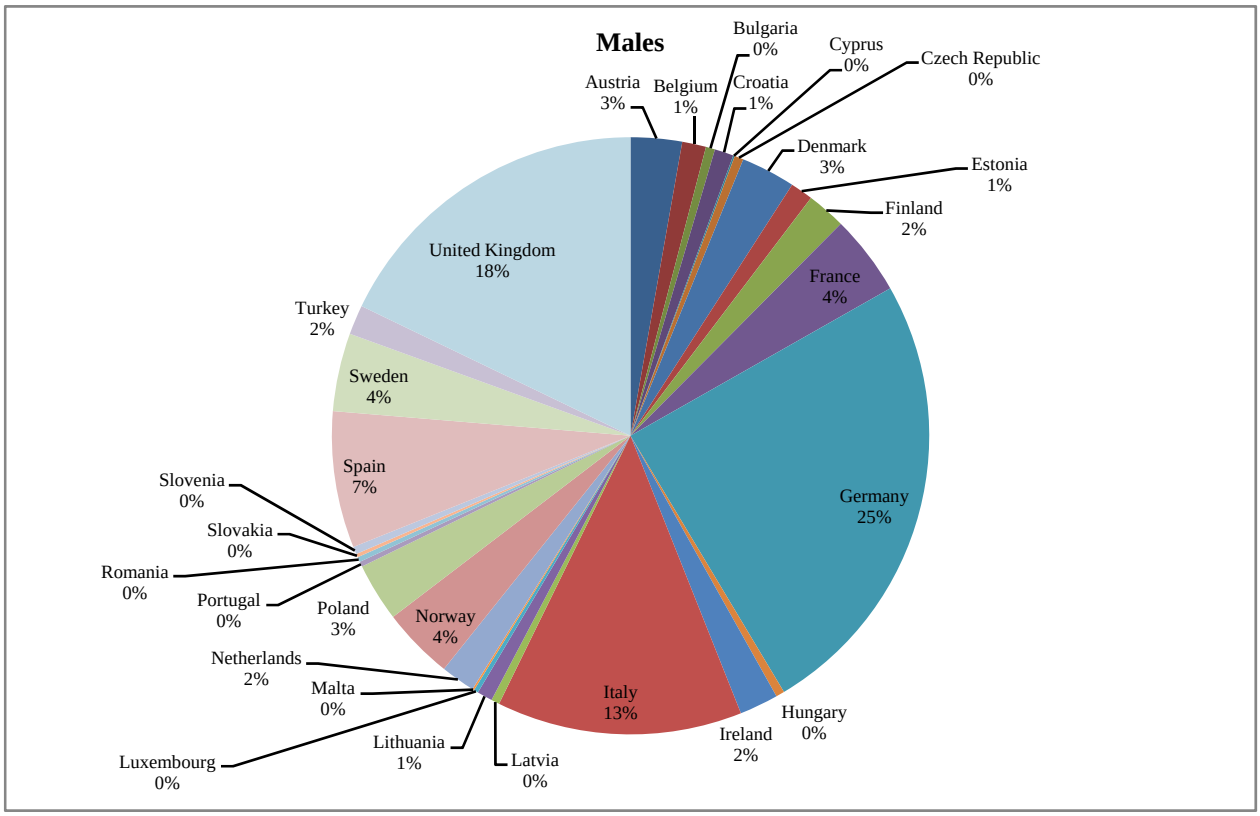
Note: Some inconsistency between total and females+males was attributed to the original recorded data of EUROSTAT.


Total population
Austria 3%
Belgium 1%
Bulgaria 0%
Croatia 1%
Cyprus 0%
Czech Republic 1%
Denmark 3%
Estonia 1%
Finland 2%
France 4%
Germany 23%
Hungary 0%
Ireland 2%
Italy 12%
Latvia 0%
Lithuania 1%
Luxembourg 0%
Malta 0%
Netherlands 2%
Norway 4%
Poland 4%
Portugal 0%
Romania 0%
Slovakia 0%
Slovenia 0%
Spain 9%
Sweden 4%
Turkey 1%
United Kingdom 18%

(a)


Females
Austria 3%
Belgium 2%
Bulgaria 0%
Croatia 1%
Cyprus 0%
Czech Republic 0%
Denmark 5%
Estonia 1%
Finland 3%
France 5%
Germany 20%
Hungary 0%
Ireland 3%
Italy 6%
Latvia 0%
Lithuania 1%
Luxembourg 0%
Malta 0%
Netherlands 2%
Norway 5%
Poland 8%
Portugal 0%
Romania 0%
Slovakia 0%
Slovenia 0%
Spain 5%
Sweden 5%
Turkey 0%
United Kingdom 24%

(b)



(c)

Fig. 1 Accumulated number of drug-induced deaths during 1995~2014: (a) total population; (b) females, and (c) males. It should be noted that the data for some countries and years were absent.

Table 2 Linear trends of drug-induced deaths recorded for three populations in European countries.

Country	Fenales						Males						Total				
	a	*b*	r^2	*F*	*p*		*a*	*b*	r^2	*F*	*p*		*a*	*b*	r^2	*F*	*p*
UK	-35449.78	17.9152	0.752	24.26	0.001	Turkey	-63711.76	31.7818	0.6083	12.42	0.008	Turkey	-66612.79	33.2303	0.594	11.69	0.009
Sweden	-16342.99	8.1824	0.897	104.40	0.000	Sweden	-29435.27	14.7865	0.8539	105.24	0.000	Sweden	-42961.39	21.5669	0.889	144.58	0.000
France	-5002.71	2.5273	0.474	14.40	0.002	Ireland	-13988.56	7.0382	0.7475	41.45	0.000	Ireland	-17782.96	8.9485	0.786	51.46	0.000
Ireland	-3794.41	1.9103	0.638	24.72	0.000	Estonia	-12774.39	6.4025	0.7019	37.67	0.000	Estonia	-14500.21	7.2673	0.728	42.86	0.000
Finland	-2195.77	1.1128	0.402	12.09	0.003	Finland	-10761.79	5.4195	0.8511	102.92	0.000	Finland	-12957.56	6.5323	0.821	82.56	0.000
Estonia	-1725.82	0.8648	0.794	61.62	0.000	Lithuania	-4981.50	2.5053	0.6811	38.44	0.000	Lithuania	-5240.76	2.6376	0.671	36.75	0.000
Netherlands	-887.93	0.4556	0.247	5.91	0.026	Romania	-3667.21	1.8357	0.5087	13.46	0.003	Romania	-4575.06	2.2893	0.639	23.03	0.000
Romania	-907.85	0.4536	0.672	26.62	0.000	Denmark	-2914.26	1.5425	0.2513	4.70	0.048	Slovenia	-1308.99	0.6656	0.271	5.96	0.027
Croatia	-745.54	0.375	0.303	6.51	0.022	Slovenia	-1151.66	0.5851	0.3013	6.90	0.018	Luxembourg	981.89	-0.4827	0.230	5.37	0.032
Hungary	718.57	-0.3553	0.228	4.71	0.045	Luxembourg	813.30	-0.4	0.238	5.62	0.029	Cyprus	1469.82	-0.7273	0.519	9.70	0.012
Czech	1339.35	-0.6636	0.401	6.02	0.037	Cyprus	1286.36	-0.6364	0.4597	7.66	0.022	Hungary	3007.92	-1.485	0.647	29.27	0.000
Spain	5368.64	-2.6357	0.496	12.79	0.003	Hungary	2111.96	-1.0407	0.6365	28.02	0.000	Czech	5809.29	-2.8703	0.532	13.63	0.003
Italy	9070.17	-4.4917	0.779	63.28	0.000	Portugal	17994.21	-8.9286	0.642	8.97	0.030	Portugal	19722.64	-9.7857	0.644	9.06	0.030
Germany	13946.26	-6.8481	0.709	43.89	0.000	Spain	53118.10	-26.2429	0.9121	134.87	0.000	Spain	43861.80	-21.5947	0.831	83.36	0.000
Norway	-2018.68	1.0361	0.174	3.36	0.086	Germany	73275.30	-35.9632	0.6776	37.83	0.000	Germany	85841.63	-42.1135	0.696	41.15	0.000
Cyprus	183.45	-0.0909	0.250	3.00	0.117	Italy	99626.33	-49.382	0.8261	85.48	0.000	Italy	108696.50	-53.8737	0.829	87.41	0.000
Austria	-938.80	0.4842	0.127	2.61	0.124	Czech	4291.53	-2.1182	0.2865	3.61	0.090	Croatia	-2757.56	1.406	0.161	3.45	0.080
Turkey	-2901.03	1.4485	0.259	2.80	0.133	Latvia	-1672.72	0.8456	0.1179	2.27	0.150	Latvia	-2167.16	1.0947	0.157	3.16	0.094
Lithuania	-259.26	0.1323	0.104	2.09	0.166	Poland	-2146.20	1.1509	0.0736	1.35	0.261	Netherlands	-2014.44	1.0624	0.120	2.46	0.134
Luxembourg	168.59	-0.0827	0.061	1.16	0.296	Bulgaria	-1243.46	0.6323	0.0967	1.93	0.182	Denmark	-2498.29	1.3701	0.137	2.22	0.158
Portugal	722.07	-0.3571	0.133	0.77	0.421	Netherlands	-1126.51	0.6068	0.0511	0.97	0.338	Bulgaria	-1452.87	0.7391	0.081	1.59	0.224
Denmark	-516.24	0.2907	0.044	0.64	0.436	Austria	-1136.97	0.6338	0.0247	0.46	0.508	UK	-40947.31	21.5091	0.156	1.48	0.259
Latvia	-170.66	0.0868	0.035	0.50	0.490	Norway	2777.46	-1.2817	0.0255	0.42	0.526	Austria	-2065.27	1.1128	0.049	0.92	0.351
Slovenia	-157.32	0.0805	0.024	0.39	0.541	Belgium	1111.27	-0.513	0.0148	0.20	0.666	France	-7245.12	3.7626	0.052	0.87	0.365
Slovakia	113.76	-0.0545	0.010	0.09	0.766	France	-2242.41	1.2353	0.0079	0.13	0.726	Norway	-3227.72	1.7404	0.029	0.51	0.483
Bulgaria	-96.75	0.0507	0.006	0.10	0.761	Croatia	-576.25	0.3162	0.0076	0.11	0.740	Poland	-1609.37	0.9298	0.017	0.29	0.597
Poland	536.83	-0.2211	0.003	0.06	0.813	UK	-5497.53	3.5939	0.0047	0.04	0.850	Malta	-74.43	0.0398	0.010	0.18	0.680
Malta	6.78	-0.0029	0.000	0.01	0.943	Slovakia	-111.48	0.0636	0.0034	0.03	0.866	Belgium	1130.85	-0.5109	0.010	0.13	0.726
Belgium	19.58	0.0022	0.000	0.00	0.996	Malta	6.26	-0.0008	0	0.00	0.993	Slovakia	2.28	0.0091	0.000	0.00	0.984
Average	-224.99	0.1353	0.010	0.18	0.675	Average	4194.53	-1.9925	0.1939	4.33	0.052	Average	4227.31	-1.9857	0.135	2.81	0.111

Red: Linear trends are tested to be statistically significant at p=0.05.

4 Discussion

In average, the number of drug-induced deaths for males in Europe declined and for females increased. Although the trends were not statistically significant, more attention may be focused on females for proper drug uses.

Some problems should be noted in further analysis and utilization of the results above: (1) the recorded number of deaths does not certainly represent the true number, due to possible missing of death cases in the survey (caused by different diagnostic tools / levels between countries, and lack of census, etc.); (2) the proportion of deaths *vs.* total inhabitants is an additional and reliable indice for evaluating the situation of drug-induced deaths, which can be included in the future.

Continuous growth of drug-induced deaths was mostly attributed to the growth of drug uses, the deteriorated medical service, or the promotion of diagnostic tools / levels, etc. However, continuous decline of drug-induced deaths was mostly attributed to the enhancement of medical service and the improvement of drug uses.

During the past years, the successful cases of drug design have been declining. The failure cases in clinical trials due to lack of drug efficacy and unexpected toxicity accounted for more than half of that in drug design (Zhang, 2016). In some therapeutic areas such as woman's health, the failure rate reaches 42% and in oncology it is as high as 30% (Booth et al., 2003). Lack of efficacy accounts for approximately 30% of failures (Kola and Landis, 2004). Moreover, many drugs are marketed and used with potential health risks. Governments and administrations should further strengthen the approval and certification of drugs. Improved drug design in reducing adverse effects is needed in the future.

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