Modeling (Multi-)Morbidity and (Poly-)Pharmacy in Outpatient Treatment with Gamma Distributions

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Abstract: Polypharmacy is often direcly causes by age and gender dependent multimorbidity. Todays treatment concepts, the individual decisions taken by physicians and the administration have to adress the complex needs of multimorbid patients. For modeling those phenomena on a collective level of an entire federal state a sufficiently large data repository is essential. The administrative bodies of the statutory health insurance in Germany have the data necessary and built up an extensive skill-set and inexpensive free-software tool-set for those evaluations. This study analyses the complete patient data of all outpatient treatments and drug prescriptions in Schleswig-Holstein (Northern German federal state) in the first quarter of 2017. Well adopted probability distributions for the frequency of diseases and drug groups decreasingly ordered within the classification system for all patients and age/gender partitions are estimated. Subsequently the levels of multimorbidity and polypharmacy (level of ICD-10/ATC-codes per quarter) are analysed in the same way. As a main result gamma distributions provide a well-adjusted model class for ICD and ATC code frequencies in the present very large routine dataset. The goodness-of-fit (full range of magnitudes of measurements) is much better than using mean values and variances.

1 INTRODUCTION

Multimorbidity and polypharmacy are major challenges for healthcare systems cf. (Dormann, H., Sonst, F., Vogler, R., Patapovas, A., Pfistermeister, B., Plank-Kiegle, B., Kirchner, M., Hartmann, N., Burkle, T. Maas, R., 2013; Fortin, M., Hudon, C., Haggerty, J., Akker, M., Almirall, J., 2010; Islam, M. M., Valderas, J. M., Yen, L., Dawda, P., Jowsey, T., McRae, I. S., 2014; Jeschke, E., Ostermann, T., Vollmar, HC, Tabali, M., Matthes, H., 2012; Glynn, L.G., Valderas, J.M., Healy, P., Burke, E., Newell, J., Gillespie, P., Murphy, A. W., 2011; Maher, R. L., Hanlon, J., Hajjar, E. R., 2014; Mitty, E., 2009; Salwe, K. J., Kalyansundaram, D., Bahurupi, Y., 2016). Costs and complications for chronic patients usually increase according to the number of comorbidities. Multimorbidity and polypharmacy are often defined by the number of diseases, disease groups, drugs or drug groups above a certain threshold value using a low number of categories. Adverse drug events, drug-drug and drug-disease interactions are strongly connected with polypharmacy cf. (Maher, R. L., Hanlon, J., Hajjar, E. R., 2014). Polypharmacy can also increase the risk of non-adherence, resulting in a suboptimal medication effectiveness and clinical consequences cf. (Glynn, L.G., Valderas, J.M., Healy, P., Burke, E., Newell, J., Gillespie, P., Murphy, A. W., 2011). If the medication non-adherence is not identified by the provider, they either increase the initial dose or add a second agent which in turn raises the health care costs and risk of adverse drug events cf. (Jeschke, E., Ostermann, T., Vollmar, HC, Tabali, M., Matthes, H., 2012). The frequency distributions for very large populations (big data) are still mostly unknown because most publications consider special diseases with sample sizes of a few hundred and up to thousand patients. Register Studies usually address special aspects with density distribution analysis cf. (Johnell, K., Klarin, I., 2007). The geriatric population is an example for high prevalence of polypharmacy associated with multiple comorbidities and advanced age cf. (Subeesh, V. K.,

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Shivaskankar, V., Gouri, N., Sriram, S., 2015; Subeesh, V. K., Gouri, N., Beulah, E. T., Shivaskankar, V., 2017). In this paper the number of different diagnoses and drug groups at certain code levels are considered as multimorbidity and polypharmacy levels for patients and the related statistical distributions are analyzed. The same approach is taken for code frequencies.

In 2017 the statutory health insurances and the associated physicians in the German federal state of Schleswig-Holstein launched expenditure controlling of outpatient prescriptions by morbidity related groups (MRG) cf. (Schuster, R., Emcke, T., Arnstedt, E.v., Heidbreder, M., 2016; Emcke, T., Ostermann, T., v. Arnstedt, E., Heidbreder, M., 2017; Schuster, R., Ostermann, T., Heidbreder, M., Emcke, T., 2018). By looking for the group with the highest drug costs on the third level ATC (four characters) within a quarter for each consulted physician and a certain patient the MRG setting takes the patient level into account. In a previous study the relations of the drug based MRG groups and diagnoses of the patients were analyzed using an age and gender standardization cf. (Schuster, R., Emcke, T., Arnstedt, E.v., Heidbreder, M., 2016).

In the present analysis the density distributions of multimorbity and polypharmacy levels as well as the ordered frequency of cases with certain ICD-10 and ATC codes are modeled by gamma distributions.

2 METHODS

We analyze all treatments and prescriptions of physicians for patients of the statutory health insurance (SHI) by SHI physicians in Schleswig-Holstein in the first quarter of 2017 without age restrictions. The analysis is patient-centered, meaning that the datasets of all treatments and prescriptions of all physicians with respect to a patient are used. The dataset covers 2,044,690 patients and 1,411,087 patients with drug prescriptions, and a pseudonymized patient ID with age and gender information. We utilize the three-character level of International Statistical Classification of Diseases and Related Health Problems [ICD]. The same diagnoses for the same patient by different physicians are not counted repeatedly. For prescription analysis the International Anatomic Therapeutic Chemical (ATC) classification system with German specifications provided by the German Institute of Medical Documentation and Information (DIMDI) is used. We analyze drug groups given by the four digit ATC (third level). The traditional approach uses summary statistics of observations, such as mean or variance, in order to find most likely probability distributions using the maximum entropy method. Frank and Smith cf. (Frank, A. S., Smith, D.E., 2010) extended this method by incorporating information about the scale of measurement. A gamma distribution has a power law shape for small magnitudes and changes to an exponential shape for large magnitudes. The scale information is included by a constraint for the maximum entropy given by an interpolation between the linear and geometric mean.

The hardware used to extract and link the data/master data is a dedicated Debian GNU/Linux Server [current generation Intel i7, 16 GByte RAM] administered by the Medical Advisory board of Statutory Health Insurance in Northern Germany.It runs a LAMP configuration (Debian GNU/Linux, Apache 2.4.29, Maria DB 10.3 [extensive use of partitioning] and PHP 7.3 [with PEAR framework esp. for spreadsheet output]).

The coding was done using the Perl programming language and the command-line tools sed/sort/awk for quick-prototyping tasks. For the statistical analysis we used Mathematica by Wolfram Research in order to get a curve fitting to a Gamma distribution for ICD and ATC drug group frequencies as well as for multimorbidity and polypharmacy frequencies. The Wolfram language and Mathematica are free when used on the small single-board computer Raspberry Pi (eg. Raspberry Pi 3 - Model B: 1,2 Ghz Quadcore - 1 GByte RAM).

The inexpensive open source/free software setup makes the cooperation of different administrative bodies possible. At the moment the hard- and software setup is able to process the data of about 6-10 Million patients.

3 RESULTS

On average the patients have 7.7 diseases at three-character ICD level (figure 1).

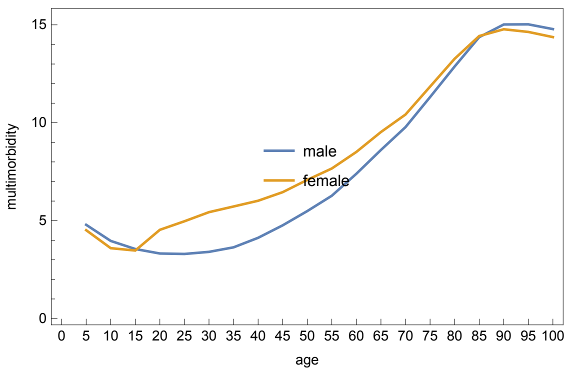

Figure 1: Age and gender dependent multimorbidity (mean values).

Patients with drug prescriptions on average have 3.2 drug groups at four digit ATC (3rd level) (figure 2).

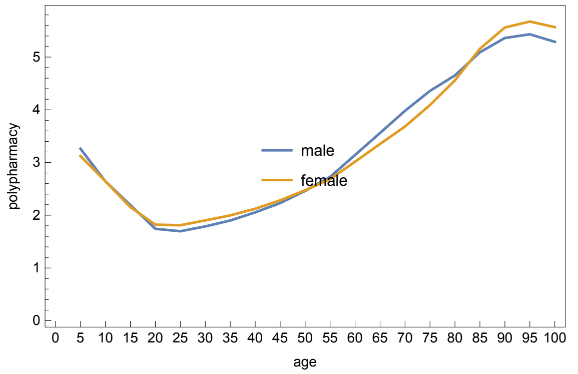

Figure 2: Age and gender dependent polypharmacy (mean values).

The curve fit to a gamma function gives the shape value of 0.4366 (0.5404) for males (females) and a decline value of 349.7 (223.0) for males (female). For women the curve fit gets worse for the most frequently used diagnoses, this effect is much weaker in men. With even smaller differences, the opposite can be stated for drug groups. This gives a shape value of 0.07833 (0.7710) for males (females) and a decline value of 24.94 (27.88) for males (females). The fit of the gamma distribution curves in figures 7,8,9 and 10 is much more exact with respect to multimorbidity and polypharmacy level (number of different codes) compared to the classification codes (ICD/ATC) considered in figures 3,4,5 and 6.

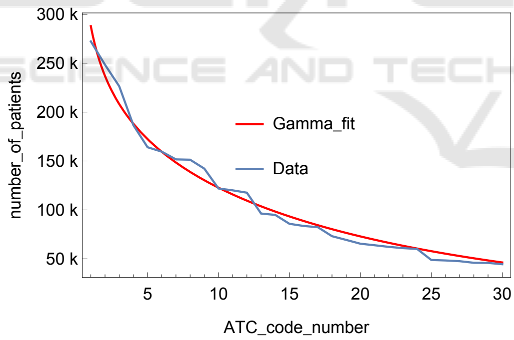

Figure 3: Curve fit (gamma function) for ATC frequencies and for small magnitudes (data (blue), gamma fit (red)).

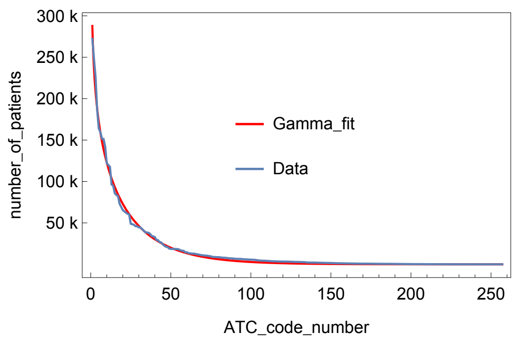

Figure 4: Curve fit (gamma function) for ATC frequencies and large magnitudes (data (blue), gamma fit (red)).

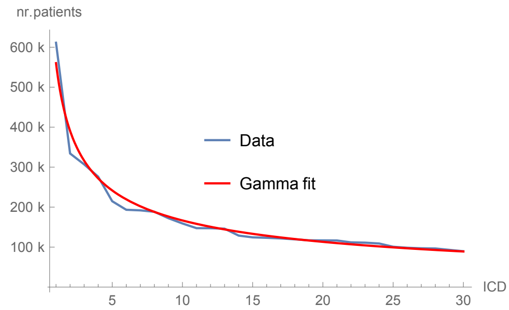

Figure 5: Curve fit (gamma function) for ICD diagnoses and for small magnitudes (data (blue), gamma fit (red)).

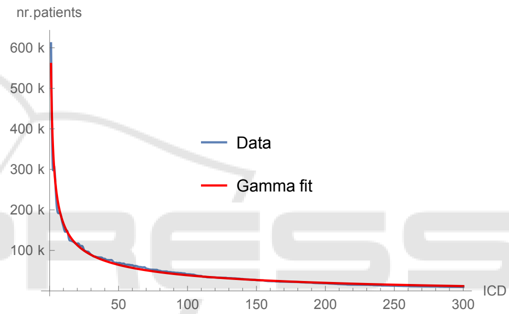

Figure 6: Curve fit (gamma function) for ICD diagnoses and large magnitudes (data (blue), gamma fit (red)).

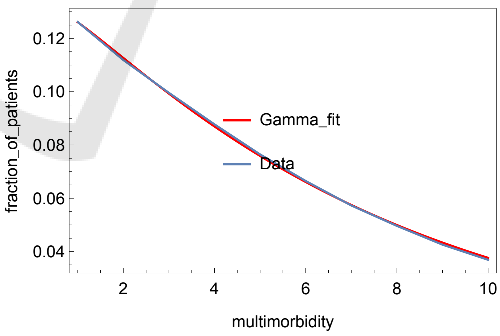

Figure 7: Curve fit for multimorbidity level (number of codes) and small magnitudes (data (blue), gamma fit (red)).

The ICD shape parameter is 1.0502 (0.9537, 1.1657) [total (male, female)] and the decline parameter has the value 6.798 (6.3856, 6.7730). The ATC shape parameter is 0.9679 (0.9982, 0.9458) and the decline parameter has the value 2.833 (2.7098, 2.8658).

The age depended mean values for the number of diagnoses (multimorbidity level) and the number of drug groups (polypharmacy level) show more gender

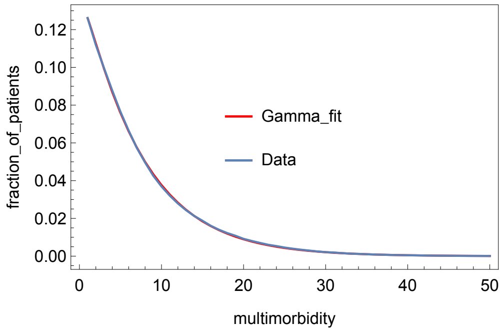

Figure 8: Curve fit for multimorbidity level (number of codes) and large magnitudes (data (blue), gamma fit (red).)

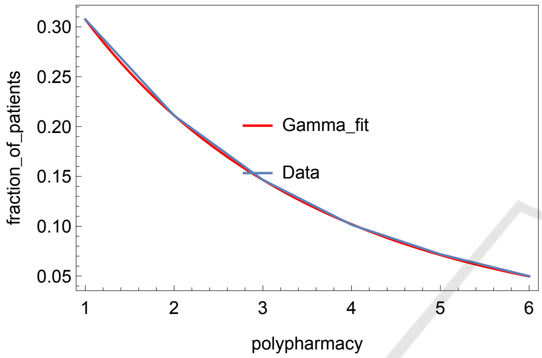

Figure 9: Curve fit for multimorbidity level (number of codes) and small magnitudes (data (blue), gamma fit (red)).

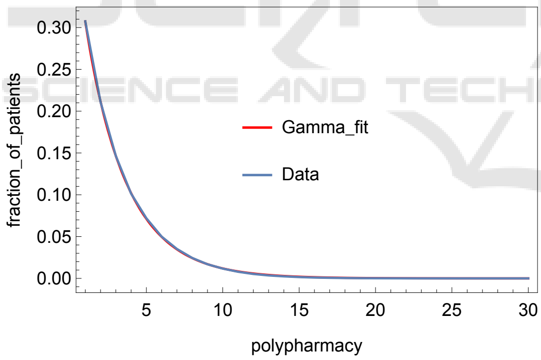

Figure 10: Curve fit for multimorbidity level (number of codes) and lage magnitudes (data (blue), gamma fit (red)).

differences with respect to diagnoses than polypharmacy.

Looking at the Top ATC/ICD positions the gender differences and the declining nature of the observations are easily observable (figures 11 and 12):

The only drug-classes where male prescriptions outweigh are ace-inhibitors, lipid modifying agents and antitrombotic drugs. In part this can be explained by the ranking and distribution of ICD-10 codes in Figure 12.

But only the good modeling results of the gamma-

pos.	nr. total	nr. male	nr. female	ATC	drug group
1	272.139	119.789	152.350	C07A	beta blocking agents
2	248.248	111.943	136.305	M01A	antiinflammatory and antirheumatic producs, non steroids
3	226.351	94.073	132.278	A02B	drugs for peptid ulcer and gastro-oesophageal reflux disease (GORD)
4	186.543	94.715	91.828	C09A	ACE inhibitors, plain
5	164.017	86.393	77.624	C10A	lipid modifying agents, plain
6	159.506	61.594	97.912	N02B	oter analgesics and antipyretics
7	151.619	79.182	72.437	B01A	antitrombotic agents
8	151.284	23.728	127.556	H03A	thyroid preparations
9	121.901	56.327	65.574	C08C	selective calcium channel blockers with mainly vascular effects
10	119.995	37.462	82.533	N06A	antidepressants

Figure 11: Top ATC positions (3rd level) by gender.

pos.	nr. total	nr. male	nr. female	ICD	disease
1	611.073	272.775	338.298	I10	Essential (primary) hypertension
2	334.167	152.057	182.110	E78	Disorders of lipoprotein metabolism
3	306.952	120.732	186.220	M54	and other lipidaemias Dorsalgia
4	276.101	129.866	146.235	J06	Acute upper respiratory infections of multiple and unspecified sites
5	214.569	84.568	130.001	H52	Disorders of refraction, accommodation
6	193.310	59.525	133.785	F32	Depressive episode
7	191.854	78.753	113.101	E66	Obesity
8	188.348	1.607	186.741	Z30	Contraceptive management
9	172.256	87.727	84.529	E11	Type 2 diabetes mellitus
10	159.089	71.618	87.471	Z00	General examination/investigation of persons without complaint, diagnosis

Figure 12: Top ICD positions (3-character level) by gender.

distribution approach enable a sound age-dependent computation of the decline as well as shape parameters for e.g. diagnoses (figures 13 and 14):

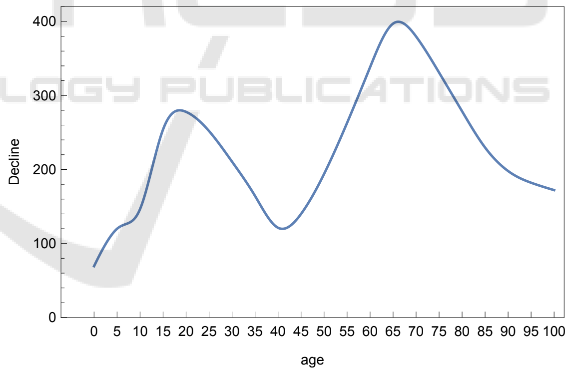

Figure 13: Age dependent decline parameter (diagnoses).

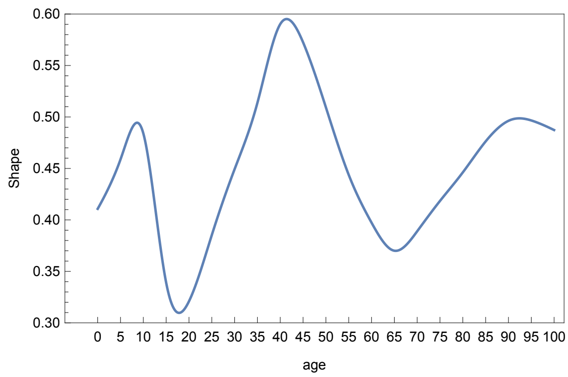

Figure 14: Age dependent shape parameter (diagnoses).

Additionally the corresponding age dependent Shannon Entropies for diagnoses and drug prescriptions are determined (figures 15 and 16):

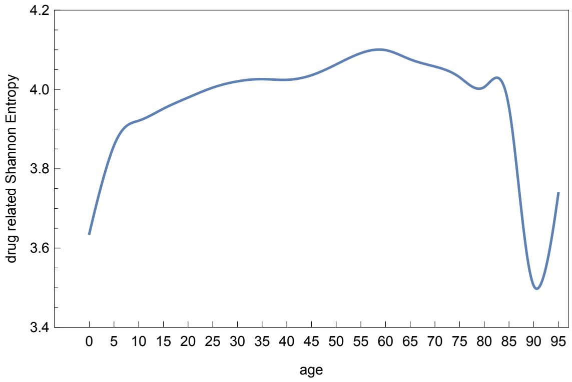

Figure 15: Age dependent Shannon Entropy (drug prescriptions).

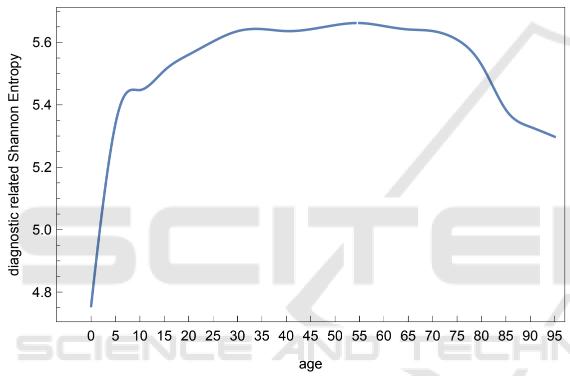

Figure 16: Age dependent Shannon Entropy (diagnoses).

4 DISCUSSION

Gamma distributions provide a well-adjusted model class for ICD and ATC code frequencies in large routine datasets. The same holds true with respect to multimorbidity and polypharmacy levels (number of codes). For small and large magnitudes the curve fitting with respect to measurements provides better results than using mean values and variances in order to determine the two parameters of the gamma distribution. In some cases the fit for intermediate values (between small and large magnitudes) might deteriorate.

There are substantial differences in the mean number of diagnoses between male and female patients, in the age group 25-29 years the females have 60 % more diagnoses on three character level of ICD than males, but only 6 % more drug groups at the four character level of ATC. Without age considerations there are 18 % more diagnoses for females, but 0.5 % fewer drug groups. Partially this is an age structure effect.

In contrast to that, there are much smaller differences in the frequency distributions of multimorbidity and polypharmacy levels among males and females, which are also gamma distributed.

5 CONCLUSIONS

Multimorbidity and polypharmacy levels have substantial impacts in health systems and policy especially against the background of demographic change. The knowledge of the underlying density distributions at different scale levels and interactions may help to organize patient oriented medical care and the healthcare marketplace.

If more than one disease and a variety of influences have to be considered, large datasets allow for the development of powerful tools. If we use the two parametric gamma distribution model, we can transform reported mean values and variations to shape and decline information and vice versa. Different scales commonly found in nature provide a general method to analyze relations between measurements, information and probability.

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