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“Advanced maternal age is associated with earlier onset of Irritable Bowel Syndrome in the offspring”

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To father and mother

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List of Abbreviations

IBS	Irritable Bowel Syndrome
GLM	General Linear Model
SES	Socio-economic status
WLS	Wisconsin Longitudinal Study

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Parental Age Effects on IBS

Advanced maternal age is associated with earlier onset of Irritable Bowel Syndrome in offspring

Abstract

Irritable Bowel Syndrome (IBS) is a very common gastrointestinal disorder presumably caused by a combination of genetic and epigenetic factors, but the exact etiology has yet to be identified. This study investigates whether the age of parents at the time of conception could have an effect on IBS. Therefore, in addition to using data from the Wisconsin Longitudinal Study, an online survey was conducted to test for potential associations between parental age at conception and both the frequency of IBS and age of offspring at onset of IBS. This study found no significant effect of parental age on the frequency of IBS in the offspring. However, a significant negative correlation was revealed between maternal age at birth and the age of offspring at the onset of IBS. This suggests that the older the mother is at conception the earlier the offspring will experience IBS. Potential theoretical explanations for this maternal age effect on IBS are presented in this paper.

Keywords

Parental Age Effect, Paternal Age Effect, Maternal Age Effect, Irritable Bowel Syndrome, Wisconsin Longitudinal Study, Age at Onset.

1. Introduction

Irritable Bowel Syndrome (IBS) is a gastrointestinal disorder affecting the large intestine with symptoms such as abdominal cramping, bloating, feeling of incomplete bowel movement, passed mucus and either diarrhea or constipation; or both at alternating intervals. Fortunately, IBS does not harm the digestive tract, but the physical discomfort and its negative effect on the patient's state of mind can impact their quality of life. (USNLM, 2014)

IBS is a very common syndrome. Worldwide, an estimated 10-15% of humans are affected (Drossman, Camilleri & Mayer, 2002), but only 5-7% are diagnosed (ACG, 2016). Statistics show that women are twice as likely to develop IBS than men (Grundmann & Yoon, 2010). Unfortunately, no cure has been developed for Irritable Bowel Syndrome, but certain medicines, diets, probiotics, changes in lifestyle and psychological therapies can reduce or even avert symptoms (NIDDK, 2013).

The causes for IBS have yet to be definitively identified. It is a very complex disorder, which is likely caused by an interaction of physical, psychological and genetic abnormalities. Moreover, an infection of the intestine can induce IBS, which is referred to as post-infectious IBS (NIDDK, 2013). For years, researchers have tried to identify a genetic component of IBS, and in 2014, Beyder et al. (2014) discovered a genetic defect that seems to be a contributor to IBS. In their research, loss-of-function mutations that disrupt the NaV1.5 channel were identified. Moreover, psychological factors such as depression, stress and anxiety are known to be crucial contributors to the etiology of IBS (Subodh, 2015). Further epigenetic factors, apart from psychological ones, are assumed to be brain-gut signal problems, gastrointestinal motor problems, hypersensitivity, bacterial gastroenteritis, small intestinal bacterial overgrowth, altered levels of neurotransmitters and food sensitivity (USNLM, 2014). Due to the complexity of IBS, the purpose of this study is to contribute to the ongoing IBS research by examining whether the age of parents at conception and its resulting consequences in the offspring play a role in the etiology of IBS.

There is an abundance of literature suggesting that parental age at conception has certain effects on the health of the offspring. Some maintain that the

older the parents are the higher the health risks for the children because diseases can accumulate, which is probably due to a rise of genetic mutations (e.g. McIntosh et al., 1995). Other studies assert that lifestyle factors can make up for these genetic drawbacks, and that being born later can compensate for biological disadvantages derived from, for instance, advanced maternal age (Barclay & Myrskylä, 2015). Regardless, it is a fact that both advanced maternal and paternal age at conception can play an adverse role in the health of the offspring.

Regarding the mother's age at birth, it is a widely held view that mothers should not postpone childbearing into their late thirties or older because genetic diseases can accumulate with advanced maternal age. Probably the best-known example of this is Trisomy 21, also known as Down Syndrome. Trisomy 21 is directly related to maternal age and its frequency in the offspring in relation to advanced maternal age is expressed in an exponential growth rate (Cuckle, Wald & Thompson, 1987).

Concerning the paternal age effect, research has been conducted in several areas. Brown et al. (2002), for example, investigated the paternal age effect regarding schizophrenia; Vestergaard, Mork, Madsen and Olsern (2005) regarding epilepsy; and Eriksen, Sundet and Tambs (2013) regarding obesity. The reason for a paternal age effect, this means an increased frequency of genetic abnormalities in the offspring in relation to the father's age, can be explained by a sex-specific difference regarding the supply of germ cells. Female germ cells, or eggs, are produced prenatally, and necessary cell divisions for prospect fertilizations are, except for the two meiotic divisions, completed by the time of birth. In contrast to this, male sperm cells are produced continuously throughout reproductive life, and, thus, the number of cell divisions increases with advanced paternal age (Vogel & Motulsky, 1979). Vogel and Motulsky (1979) suggest that every ten years about 230 divisions are added, concluding that sperm cells of, for instance, a 28-year old man, have gone through 380 chromosome replications. When comparing this number with a 35-year old man with 540 chromosome replications, it becomes clear that the probability of mutations to occur increases drastically (Crow, 2000). Other factors such as a reduced fidelity of DNA replication or decreased efficiency of repair mechanisms with

age are expected to add to this effect (Crow, 2000). Therefore, it can be concluded that the number of “de novo mutations” in aging men increases, and thereby the chance of transmitting a deleterious mutation to the offspring increases accordingly (Kong et al., 2012). Considering maternal age, an explanation regarding an increased number of pre-meiotic cell divisions cannot be given. However, Crow (2002), for instance, suggests that the duration for which the chromosomes are “suspended” in meiosis could be a cause for maternal age effects.

Accordingly, since mutations accumulate with parental age (Vogel & Motulsky, 1979) and IBS is assumed to have a genetic component (Beyder et al., 2014), this paper considers possible an association between the parental age effect and the frequency of IBS in the offspring. If such an association exists, it could be regarded as another clue for a genetic component of IBS. Furthermore a possible correlation between age of parents at conception and the age of offspring at the onset of IBS is explored. Since IBS is a complex syndrome and epigenetic factors may also play a crucial role in the etiology of IBS, it is here hypothesized that the age of parents at conception might also have an effect on the development of IBS independently of genetics. For example, maternal age is often associated with increased rates of caesarean sections (Peipert & Bracken, 1993), and studies suggest that C-sections increase the risk for atopic diseases (Penders et al., 2007) or allergies and asthma in the offspring (Bager et al., 2008; Negele et al., 2004). Thus, a possible correlation between C-sections and IBS is also investigated. All in all, the ultimate goal of this paper is to investigate a potential effect of the paternal and the maternal age at conception on the frequency and age at onset of IBS in the offspring.

2. Material and methods

The data utilized to test the hypothesis was derived from two sources; the first of which was the Wisconsin Longitudinal Study (WLS) and the second was a self-made online-survey with respondents primarily from western societies.

The Wisconsin Longitudinal Study is a long-term study collecting samples of 10,317 male and female graduates from Wisconsin high schools in 1957. Respondents were asked to answer questions about several areas of their

life, including physical and mental health (Herd et al., 2014). It is possible to extract information about IBS such as whether there has been a diagnosis and age at time of diagnosis. Associations were then checked between these key variables and factors including parental age and socio-economic status.

Furthermore, we created a questionnaire on [freeonlinesurveys.com](https://www.freeonlinesurveys.com) and used the social media platform Facebook to solicit people to participate in the survey. People suffering from IBS were sought out to complete the survey by engaging members in relevant groups such as “IBS Support,” “Help for Irritable Bowel Syndrome- Heather’s Tummy Care for IBS” and “Food Intolerance, IBS and Autoimmune Support.” Thereby, information about IBS was collected and correlations and regressions between key variables and parental age and socio-economic status as a child were checked. Furthermore, in order to check for a relationship between C-sections and IBS, information was collected regarding the circumstances of the birth of survey respondents.

In total there were 213 responses to the survey. We are aware that because the data were collected via Facebook groups there is the risk that potential respondents were preselected. First, internet access varies across social classes, and studies suggest that more affluent people are more likely to take part in surveys (Goyder, Warriner, & Miller, 2002). Second, women are more likely to complete questionnaires (Moore & Tarnai, 2002), which is reflective of this study, as the majority of respondents were female (91%). However, this is to be somewhat expected because women are more often affected by IBS (Grundmann & Yoon, 2010).

With respect to the nationality of respondents, the majority of respondents were from Britain, America, Austria, Australia, Canada (69%) and other western countries. Therefore, the survey should be regarded as presenting information about IBS in western societies. Nevertheless, since studies such as Gwee (2005) suggest that IBS is “highly prevalent in western societies such as the UK and USA”, we consider the choice of data, both that of the Wisconsin Longitudinal Study (USA) and the online-questionnaire to be appropriate to test the proposed hypothesis.

For statistical analysis we used SPSS Statistics 23. Variables such as father's age at birth, mother's age at birth, whether diagnosed with IBS, age diagnosed with IBS, type of delivery and socio-economic status (SES) were all tested for associations. To determine potential associations between key variables we calculated bivariate correlation and performed several general linear models. The WLS dataset provided variables such as gender, father's age at birth, mother's age at birth, socio-economic status, whether diagnosed with IBS or not and age at onset of IBS. The online survey provided for father's age at birth, mother's age at birth, financial status at patient's childhood, age at onset of IBS and type of delivery.

Accordingly, we regressed predicative factors and covariates such father's age at birth, mother's age at birth, SES and type of delivery with dependent variables such as whether diagnosed with IBS and age at onset of IBS (on basis of binominal error structure). Moreover, we calculated bivariate correlations (Pearson R and Spearman's Rho) between key variables such as father's age at birth, mother's age at birth and age diagnosed with IBS.

3. Results

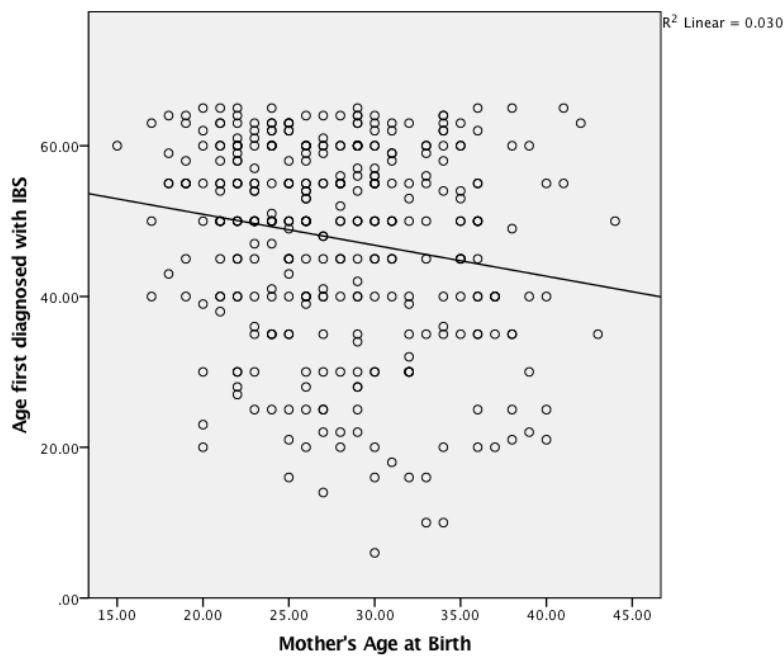
The analysis of the Wisconsin Longitudinal Study Data revealed that out of 6639 valid respondents 616 have been diagnosed with IBS, which calculates to 9.3%. When considering the gender ratio of the IBS data, a significantly higher number of women are affected by IBS. According to the WLS data, women are 2.5 times more likely to develop IBS (443 female IBS patients vs. 173 male IBS patients, at a relatively equal percentage of responses per sex). This gender ratio is also displayed in the GLM in Table 1 revealing a negative significant regression coefficient of -0.841 (sig. 0.000; male reference) that points to a female majority of IBS patients. The regression of the GLM also revealed that neither age of father nor age of mother at birth seem to have a significant effect on the frequency of IBS in the offspring (Table 1). Furthermore, the socio-economic status of the patient's family does not seem to have a significant effect on the frequency of IBS (Table 1).

Table 1. General Linear Model of key variables on frequency of IBS (WLS Data).

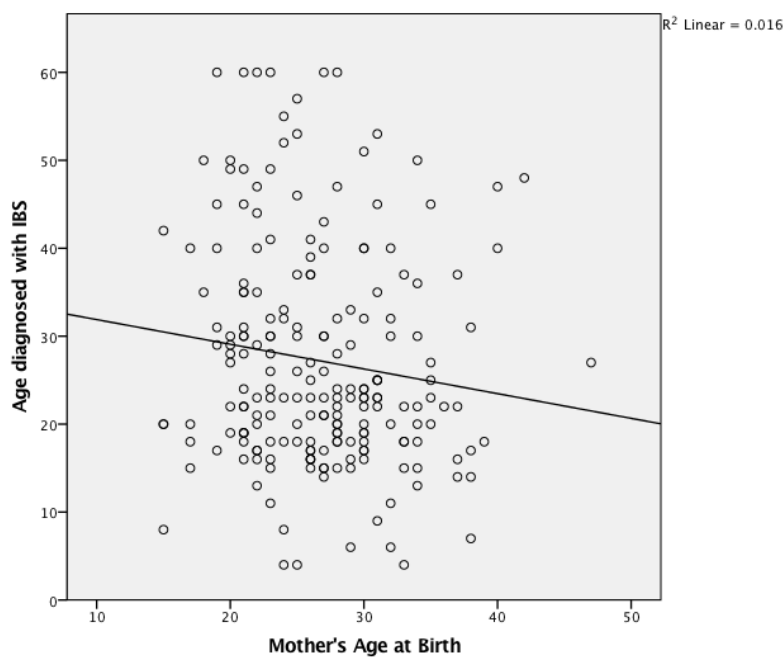
	B	Std.Error	p
Intercept	-1.764	0.2615	0.000
Sex (reference: male)	-0.841	0.1049	0.000
Father's age at subject's birth	0.003	0.0111	0.813
Mother's age at subject's birth	-0.012	0.0127	0.357
Socio-Economic Status	0.003	0.0042	0.416

When further exploring the parental age effect on IBS we were able to identify a different impact. The age of parents negatively correlates with the age of offspring at the onset of IBS. The calculation of a Pearson correlation with the WLS Data between the paternal age at birth and age of child at onset of IBS resulted in a significant, slightly negative correlation (N = 360, Pearson R = -0.107, P = 0.042) between these variables. This suggests that the older the father is at conception the younger the child at the onset of IBS. However, when testing the correlation with the Online Survey Data no significance was found between the two variables (N = 201, Pearson R = -0.088, P = 0.215). Hence, these two independent datasets cannot confirm a paternal age effect on IBS, neither on frequency nor age at onset of IBS.

On the other hand, maternal age seems to have a significant effect on the age at onset of IBS, which is supported by both datasets. Again, calculating bivariate correlations with the WLS Data (N = 350, Pearson R = -0.173, P = 0.001) and the Online Survey Data (N = 205, Spearman's Rho = -0.151, P = 0.031) displayed a significant negative correlation. Taking these two correlations into consideration, it appears that the older the mother at conception the earlier the children will develop IBS. This association between maternal age and earlier onset of IBS in the offspring is visualized in Graphs 1 and 2.



Graph 1. Scatter plot and linear regression on age first diagnosed with IBS and mother's age at birth (WLS Data).



Graph 2. Scatter plot and linear regression on age first diagnosed with IBS and mother's age at birth (Online Survey Data).

Finally, when considering key variables such as gender, paternal age, maternal age and socio-economic status in a General Linear Model collectively (using WLS Data), it demonstrates that maternal age is, in fact, an effective and significant variable influencing the age at diagnosis of IBS (Table 2). The GLM regressing the data of our online survey, however, did not reveal such an effect (Table 3). None of the variables in the model are significantly associated with the age of the offspring at diagnosis of IBS.

Table 2. General Linear Model of key variables on age diagnosed with IBS (WLS Data).

	B	Std.Error	p
Intercept	57.556	3.8790	0.000
Sex (reference: male)	2.278	1.6074	0.156
Father's age at subject's birth	0.181	0.1810	0.318
Mother's age at subject's birth	-0.567	0.2010	0.005
Socio-Economic Status	-0.017	0.0583	0.771

Table 3. General Linear Model of key variables on age diagnosed with IBS (Online Survey Data).

	B	Std.Error	p
Intercept	29,077	5,7032	0.000
Sex (reference: male)	-4,116	3,2759	0,209
Father's age at subject's birth	-0,057	0,1929	0,768
Mother's age at subject's birth	-0,158	0,2292	0,489
Type of Delivery (reference: vaginally)	2,854	2,5184	0,257
Financial Status as child (reference: poor)	0,717	3,7062	0,847

Additionally to a parental age-related exploration of our IBS datasets, we regressed the age at onset of IBS with the socio-economic status of the IBS patients. Our calculated General Linear Models do not show any

associations between the socio-economic status and the frequency of IBS in the offspring (Table 1) or the age at onset of IBS, neither using the WLS Data (Table 2) nor our Online Survey Data (Table 3).

The last regression investigated was the type of delivery with the age at onset of IBS. Regressing a GLM of the variable “Age diagnosed with IBS” against “Type of Delivery” was intended to test whether C-sections influence the age at onset of IBS. No significance was found in the regression (Table 3).

4. Discussion

The data revealed that neither age of father nor mother at birth seem to have a significant effect on the frequency of IBS in the offspring. A child's development of IBS appears to be independent of their parents' age. The datasets could not confirm any effect of paternal age on frequency or age at onset of IBS in the offspring. Since mutations tend to accumulate with advanced paternal age, a paternal age effect on the frequency of IBS in the offspring could have been an indicator for a genetic component of the Irritable Bowel Syndrome. However, this study was not able to corroborate a genetic component of IBS due to an increase of mutations influenced by the father's age. To be clear it should not be considered a refutation of the importance of genetics in the etiology of IBS, since exceptions to the paternal age effect do exist (see Crow, 2000).

However, this study was able to detect a significant negative correlation between maternal age and the age of offspring at onset of IBS. This suggests that the older the mother at birth the earlier the child will develop IBS. A regression coefficient of -0.567 (sig. 0.005) (see Table 2) suggests that every advancing year of the mother's age statistically results in the onset of IBS in the offspring occurring roughly half a year earlier.

Maternal age effects on the age at onset were also detected in correlation with other disorders. Bingley et al. (2000) assert that advanced maternal age at birth may also correlate with an earlier onset of type 1 diabetes in the offspring. Of course, the mother's age itself cannot influence the etiology of disorders; but factors that change with advanced maternal age could.

Accordingly, it should be the aim of this paper, but also of future researchers, to identify these factors.

It is a complex issue to predict factors that influence the age at onset of IBS, especially in correlation with the mother's age. Since genetics might have resulted in a rise of frequency of IBS in the offspring due to increased rates of replication defects (Crow, 2002), this paper posits that an earlier onset of the disorder may be the result of epigenetic factors.

Therefore, we also tested whether the socio-economic status, which tends to change with the parents' age, may have an effect on the age at onset of IBS, but the results revealed no such relation. This suggests that the socio-economic status does not influence the development of IBS.

A possible theory that could potentially explain the maternal age effect on the onset of IBS is adverse perinatal outcomes, which statistically accumulate with advanced maternal age (Kenny et al., 2013). Bengtson et al. (2006) tested whether birth weight had an influence on the development of IBS. Their twin-study revealed that those babies with a birth weight below 1500g were not only more likely to develop IBS but also to experience onset at a younger age. Since only four of the participants in our online-survey indicated their birth-weight as below 1500g, it was not possible to retest Bengtson et al.'s results, indicating a potential limitation of our study. Furthermore, Kwang-sun et al. (1988) suggest an increased risk for low birth weight with advancing maternal age and cite a "decreased potential for fetal growth" as a possible reason. Also, Karn and Penrose (1951) detected a slight maternal age effect regarding low birth weight. This suggests that a correlation between maternal age and a younger onset of IBS in the offspring could possibly be explained by deviations in birth weight.

Furthermore, the frequency of a factor that can appear in connection with low birth weight also increases sharply with advanced maternal age: preterm deliveries (Astolfi & Zonta, 1999). It might be conceivable that the factor pre-term delivery also correlates with an earlier onset of IBS. Berseth (1989) investigated the influence of gestational age on the motility of the small intestine and reported that the intestinal motor activity is less developed in preterm babies. Thus, "gut immaturity" (Bengtson et al., 2006) derived from

pre-term delivery, could possibly also affect the large intestine and be a reason for an earlier onset of IBS.

Another theory tested during the data exploration was the impact of the type of delivery on the development of IBS, since advanced maternal age is associated with a higher number of Caesarean deliveries (Peipert & Bracken, 1993). Studies propose a risk-increasing effect of Caesarean sections on allergies and asthma (Bager et al., 2008; Negele et al., 2004), childhood obesity (Huh et al., 2012), inflammatory bowel disease and immune deficiencies (Sevelsted et al., 2015) and other disorders. A possible reason for a risk-increasing effect could be an altered microbiome in the offspring derived from C-sections (Selvested et al., 2015). Unfortunately, it was not possible to test whether C-sections have a direct impact on the frequency of IBS, since neither of the datasets allowed for the calculation of the correlation of those variables and compare them to healthy C-section control subjects. It is only possible to consider those respondents to our online questionnaire who were delivered by C-sections, and point out that a prevalence of 14% does not seem to be a strikingly high number. However, it was possible to test whether C-sections have a statistical effect on the age at onset of IBS, but this analysis did not reveal any significant effect (Table 3).

In conclusion, IBS appears to be influenced by the mother's age at conception. More precisely, advanced maternal age seems to have a reverse effect on the age of offspring at onset of IBS. Epigenetic factors that can change with advanced maternal age and could have an effect on the age at onset of IBS have been pointed out. They can be investigated in future research.

Additionally, the data was collected through interviews and questionnaires, and, thus, the accuracy of respondents' answers could not be validated. Moreover, both the Wisconsin Longitudinal Study as well as the online survey were asking respondents to indicate their age at diagnosis. This might deviate from the age they first developed symptoms of IBS. There might be a time lag between the first symptoms and consulting a doctor. Moreover, the process of diagnosing IBS requires time because it is made by excluding other disorders. This could influence the outcomes of the data, which suggests that the findings of this paper are without guarantee.

As a last point, we suggest that more research beyond mere statistical analysis should be devoted to identifying factors that influence the development and age at onset of IBS. Moreover, since IBS is not curable as of yet, there is every hope that future studies investigate potential treatments for IBS, since the lives of about 15% of the world's population could be improved through more successful remedies.

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6. References

- American College of Gastroenterology (ACG). (2016). Irritable bowel syndrome. Available at www.patients.gi.org/topics/irritable-bowel-syndrome. (accessed 31 March 2016).
- Astolfi, P. & Zonta, L. A. (1999). Risks of preterm delivery and association with maternal age, birth order, and fetal gender. *Human Reproduction*, 14, 2891-2894.
- Bager, P., Wohlfahrt, J. & Westergaard, T. (2008). Caesarean delivery and risk of atopy and allergic disease: meta-analyses. *Journal for the British Society for Allergy and Clinical Immunology*, 38, 634 - 642.
- Barclay, K. & Myrskylä, M. (2015). Advanced maternal age and offspring outcomes: causal effects and countervailing period trends. *MPIDR Working Paper 009*, Rostock: Max-Planck-Institute for Demographic Research.
- Bengtson, M. B., Rønning, T., Vat, M. H. & Harris, J. R. (2006). Irritable bowel syndrome in twins: genes and environment. *Gut*, 55, 1754–1759.
- Berseth, C. L. (1989). Gestational evolution of the small intestine motility in preterm and term infants. *Journal of Paediatrics*, 115, 646–651.
- Beyder, A., Mazzone, A., Strege, P. R., Tester, D. J., Saito, Y. A., Bernard, C. E., Enders, F. T., Ek, W. E., Schmidt, P. T., Dlugosz, A., Lindberg, G., Karling P., Ohlsson, B., Gazouli, M., Nardone, G., Cuomo, R., Usai-Satta, P., Galeazzi, F., Neri, M., Portincasa, P., Bellini, M., Barbara, G., Camilleri, M., Locke, G. R., Talley, N. J., D'Amato, M., Ackerman, M. J. & Farrugia, G. (2014). Loss-of-function of the voltage-gated sodium channel $Na_v1.5$ (Channelopathies) in patients with irritable bowel syndrome. *Gastroenterology*, 146, 1659-1668.
- Bingley, P. J., Douek, I. F., Rogers, C. A. & Gale, E. A. (2000). Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. *BMJ*, 321 (7258), 420-424.
- Brown, A. S., Schaefer, C. A., Wyatt, R. J., Begg, M. D., Goetz, R., Bresnahan, M. A., Harkavy-Friedman, J., Gorman, J. M., Malaspina, D. & Susser, E. S. (2002). Paternal age and risk of schizophrenia in adult offspring. *American Journal of Psychiatry*, 159, 1528–1533.
- Crow, J. F. (2000). The origins, patterns and implications of human spontaneous mutation. *Nature Review Genetics*, 1, 40–47.

- Cuckle, H.S., Wald, N. J. & Thompson, S. G. (1987). Estimating a woman's risk of having a pregnancy associated with down's syndrome using her age and serum alpha-fetoprotein level. *British Journal of Obstetrics and Gynaecology*, 94, 387-402.
- Drossman, D. A., Camilleri, M., Mayer, E. A. & Whitehead, W. E. (2002). AGA technical review on irritable bowel syndrome. *Gastroenterology*, 123, 2108–2131.
- Eriksen, W., Sundet, J. M., & Tambs, K. (2013). Paternal age at birth and the risk of obesity in young adulthood: a register-based birth cohort study of norwegian males. *American Journal of Human Biology*, 25, 29–34.
- Goyder, J., Warriner, K., & Miller, S. (2002). Evaluating socio-economic status (SES) bias in survey nonresponse. *Journal of Official Statistics*, 18 (1), 1–11.
- Grundmann, O. & Yoon, S. L. (2010). Irritable bowel syndrome: epidemiology, diagnosis, and treatment: an update for health-care practitioners. *Journal of Gastroenterology and Hepatology*, 25, 691–699.
- Gwee. K. A. (2005). Irritable bowel syndrome in developing countries – a disorder of civilization or colonization?. *Journal of the Neurogastroenterology and Motility Society*, 17, 317–324.
- Herd, P., Carr, D., & Roan, C. (2014). Cohort profile: Wisconsin Longitudinal Study (WLS)." *International Journal of Epidemiology*, 43, 34-41.
- Huh, S. Y., Rifas-Shiman, S. L., Zera, C. A., Edwards, J. W., Oken, E., Weiss, S. T. & Gillman, M. W. (2012). Delivery by caesarean section and risk of obesity in preschool age children: a prospective cohort study. *Archives of Disease in Childhood*, 97, 610-616.
- Karn, M. N. & Penrose, L. S. (1951). Birth weight and gestation time in relation to maternal age, paternity and infant survival. *Annals of Eugenics*, 16 (1), 147-164.
- Kenny, L., Lavender, T., McNamee, R., O'Neill, S. M., Mills, T. & Kashan A. S. (2013). Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. *PLoS ONE*, 8(2). e56583. doi:10.1371/journal.pone.0056583.
- Kong, A., Frigge, M. L., Masson, G., Besenbacher, S., Sulem, P., Magnusson, G., Gudjonsson, S. A., Sigurdsson, A., Jonasdottir, A., Wong, A. S.,

- Sigurdsson, G., Walters, G. B., Steinberg, S., Helgason, H., Thorleifsson, G., Gudbjartsson, D. F., Helgason, A., Magnusson, O. T., Thorsteinsdottir, U. & Steffansson, K. (2012). Rate of de novo mutations and the importance of father's age to disease risk. *Nature*, 488, 471–475.
- Kwang-sun, L. Ferguson, R. M., Corpuz, M. & Garnter, L. M. (1988). Maternal age and incidence of low birth weight at term: a population study. *American Journal of Obstetrics and Gynaecology*, 158, 84-89.
- McIntosh, G. C., Olshan, A. F. & Baird, P. A. (1995). Paternal age and the risk of birth defects in offspring. *Epidemiology*, 6 (3), 282-288.
- Moore, D. L., & Tarnai, J. (2002). Evaluating nonresponse error in mail surveys. In: Groves, R. M., Dillman, D. A., Eltinge, J. L., and Little, R. J. A. (eds.), *Survey Nonresponse*, John Wiley & Sons, New York, 197–211.
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). (2013) Irritable bowel syndrome - national digestive diseases information. *Clearinghouse. NIH Publication*, 13 (693). Available at http://www.niddk.nih.gov/health-information/health-topics/digestive-diseases/irritable-bowel-syndrome/Documents/ibs_508.pdf (accessed 31 March 2016).
- Negele, K., Heinrich, J., Borte, M., von Berg, A., Schaaf, B., Wichmann, H. E., Bolte, G. & LISA Study Group. (2004). Mode of delivery and development of atopic disease during the first 2 years of life. *Pediatric Allergy and Immunology*, 15, 48–54.
- Peipert, J. F. & Bracken, M. B. (1993). Maternal age: an independent risk factor for cesarean delivery. *Obstetrics & Gynaecology*, 81 (2), 200-205.
- Penders, J., Thijs, C., van den Brandt, P. A., Kummeling, I., Snijders, B., Stelma, F., Adams, H., van Ree, R. & Stobberingh, E. E. (2007). Gut microbiota composition and development of atopic manifestations in infancy: the KOALA birth cohort study. *Gut*, 56, 661–667.
- Selvested, A., Stokholm, J., Bønnelykke, K. & Bisgaard, H. (2015). Cesarean section and chronic immune disorders. *Pediatrics*, 135 (1), 92-98.
- Subodh, K. L. (2015). Irritable bowel syndrome. *U.S. National Library of Medicine*. Available at <https://www.nlm.nih.gov/medlineplus/ency/article/000246.htm> (accessed 31 March 2016).

- U.S. National Library of Medicine (USNLM) - MedlinePlus. (2014). Irritable bowel syndrome. Available at <https://www.nlm.nih.gov/medlineplus/irritablebowelsyndrome.html> (accessed 31 March 2016).
- Vestergaard, M., Mork, A., Madsen, K. M., & Olsern, J. (2005). Paternal age and epilepsy in the offspring. *European Journal of Epidemiology*, 20, 1003–1005.
- Vogel, F. & Motulsky, A. G. (1979). Human genetics: problems and approaches. Berlin: Springer Verlag.

Appendix

I. Summary in German & English

Das Reizdarm-Syndrom ist eine Störung der Darmaktivität, welche sehr wahrscheinlich durch Zusammenwirken von genetischen und epigenetischen Faktoren ausgelöst wird. Diese Einflussfaktoren sind jedoch noch nicht zur Genüge erforscht. Daher wurde in dieser Diplomarbeit der Einflussfaktor „Alter der Eltern bei Geburt“ in Zusammenhang mit dem Reizdarmsyndrom getestet. Dazu wurden Daten von der Wisconsin Longitudinal Study analysiert und zusätzlich eine Online-Befragung von an Reizdarmsyndrom erkrankten Personen durchgeführt. Potentielle Zusammenhänge zwischen dem Alter der Eltern bei Zeugung des Kindes und der Häufigkeit des Syndroms in den Nachkommen wurde getestet. Weiters wurden auch Korrelationen zwischen dem parentalen Alter und dem Alter des Kindes bei Auftreten der Symptome erforscht. Unsere statistische Analyse der Daten hat keinen Zusammenhang zwischen Alter der Eltern bei Geburt und Häufigkeit der Krankheit in den Nachkommen aufgezeigt. Dies bedeutet, dass das fortschreitende Alter der Eltern scheinbar keinen Einfluss darauf hat, ob das Kind das Reizdarm-Syndrom entwickelt oder nicht. Nichtsdestotrotz, konnte eine negative Korrelation zwischen dem Alter der Mutter bei Geburt und dem Alter der Kinder bei Auftreten des Syndroms erforscht werden. Desto älter die Mutter bei der Geburt ist, desto früher scheint der Nachwuchs vom Reizdarm-Syndrom betroffen zu sein. Potentielle Theorien, die diese Korrelation erklären könnten, wie zum Beispiel verfrühte Geburt des Kindes bzw. geringeres Geburtsgewicht, welche sich statistisch bei älteren Müttern häufen, wurden in dieser Diplomarbeit präsentiert.

Irritable Bowel Syndrome (IBS) is a very common gastrointestinal disorder presumably caused by a combination of genetic and epigenetic factors, but the exact etiology has yet to be identified. This study investigates whether the age of parents at the time of conception could have an effect on IBS. Therefore, in addition to using data from the Wisconsin Longitudinal Study,

an online survey was conducted to test for potential associations between parental age at conception and both the frequency of IBS and age of offspring at onset of IBS. This study found no significant effect of parental age on the frequency of IBS in the offspring. However, a significant negative correlation was revealed between maternal age at birth and the age of offspring at the onset of IBS. This suggests that the older the mother is at conception the earlier the offspring will experience IBS. Potential theoretical explanations for this maternal age effect on IBS are presented in this paper.

II. IBS Questionnaire for Participants

Irritable Bowel Syndrome Questionnaire

Dear IBS-Patients! Thank you for participating in this survey. Please answer the following questions. If you are not sure about any answer, try to give a rough answer. If you do not know the answer at all, please leave out the question.

Information for question 10: conversion into pounds:

- less than 1499g (less than 3.3 pounds)
- 1500-1999g (3.3-4.4 pounds)
- 2000-2499g (4.4-5.5 pounds)
- 2500-2999g (5.5-6.6 pounds)
- 3000-3499g (6.6-7.7 pounds)
- more than 3500g (more than 7.7 pounds)

1 Are you male or female? ☐ male ☐ female

2 How old are you?

3 What is your nationality?

4 How old had you been when first being diagnosed with IBS?

5 How old was your father at your birth?

6 How old was your mother at your birth?

7 Which type of IBS do you have?

- ☐ diarrhea-predominant
 - ☐ constipation-predominant
 - ☐ alternating stool pattern
-

8 What was your type of delivery (how were YOU born)?

- ☐ vaginally
☐ cesarean delivery
-

9 Had you been delivered too early (= preterm birth)?

- ☐ No
☐ Yes: moderate to late preterm (32 to <37 weeks)
☐ Yes: very preterm (28 to <32 weeks)
☐ Yes: extremely preterm (<28 weeks)
-

10 What was your birth weight?

- ☐ less than 1499g
☐ 1500-1999g
☐ 2000-2499g
☐ 2500-2999g
☐ 3000-3499g
☐ more than 3500g
-

11 How would you rate your psychological well-being as a child?

- ☐ Poor ☐ Fair ☐ Neutral ☐ Good ☐ Excellent
-

12 How would you rate your financial family condition as a child?

- ☐ Poor ☐ Fair ☐ Neutral ☐ Good ☐ Excellent
-

Thank you for your participation and good luck and health for your future! Elisabeth