Suppl. Methods and Results

Definition of age-dependent reference values for the diameter of the common bile duct and pancreatic duct on MRCP: a population-based, cross-sectional, cohort study

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Suppl. Methods

Study population

Baseline examinations in the SHIP-Start cohort (SHIP-Start-0) were conducted between 1997 and 2001 in 4,308 inhabitants of the study region West Pomerania. All participants from SHIP-Start-0 were invited to participate in four follow-ups (SHIP-Start-1 to SHIP-Start-4). Baseline examinations in the SHIP-Trend cohort (SHIP-Trend-0), an independent population-based cohort in the same study region, were conducted between 2008 and 2012 in 4,420 subjects.

Of the initial 4,308 SHIP-Start-0 participants, 2,333 subjects agreed to participate in SHIP-Start-2. SHIP-Trend-0 recruited a total of 4,420 subjects [1]. In SHIP-Start-2 and SHIP-Trend-0, that represent the baseline of the study presented here, MRI and MRCP were performed upon informed consent [2, 3] and a total of 3,369 participants eventually underwent wholebody MRI [3]. The follow-up data presented here is based on SHIP-Start-3 and SHIP-Trend-1 data. SHIP-Start-3 started in 2014 and finished in 2016, while SHIP-Trend-1 started in 2016 and finished in 2019. Of the 1,018 subjects included in the cross-sectional analyses, 40 died and 191 were lost to follow-up, leaving 787 with sufficient follow-up data available. For details, please see **Figure 1** and **suppl. Figure 1**.

MR Technique, Study Medication and Protocol for Incidental Findings

We used a 1.5-T MRI system (Magnetom Avanto, Siemens Healthcare). The MRCP (navigator-triggered T2-weighted 3D turbo spin-echo) included an automatic maximum-intensity-projection (MIP) reconstruction in the coronal orientation using the following imaging parameters: TR, approximately 900 ms; long TE, 742 ms; bandwidth, 260 Hz/pixel; matrix, 384 × 384; number of slices, 44; and slice thickness 1.5 mm. The acquisition for MRCP varied between 2 to 6 minutes depending on subject size. For those receiving secretin, an unstimulated MRCP was obtained first, followed by a scan after secretin administration (Secrelux®, Sanochemia Pharmazeutika AG) in the same orientation. Secretin was administered at 1 U/kg of body weight, slow injection over 60 seconds and was followed by a 20-mL saline flush as described previously.[2, 4, 5]

For MRI examinations an additional consent form was developed in which the study participant could opt for a full report of all findings, decline any information on the findings or only being informed about potentially life threating findings. All incidental findings were discussed by a multidisciplinary advisory board and in case follow up investigations were recommended and the study participant had opted to be informed on the findings, the participant and primary

Beyer G, *et al. Gut* 2023; 72:1738–1744. doi: 10.1136/gutjnl-2021-326106

physician were contacted to pursue further diagnostic work-up, however the results of such work-up were not available for analysis.[6] This strategy has been adopted by the German national cohort study.[7] A relevant negative effect of this strategy on mental health of the study participants has been excluded.[8] A full list of data available from SHIP cohorts including MRI-data can be found here: https://www.fvcm.med.uni-greifswald.de/dd_service/data_use_explore.php?lang=ger, a full report on study related examinations has been reported elsewhere. [9]

Laboratory Analyses

Serum activities of alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma glutamyl transferase (GGT), amylase, and lipase were determined photometrically on the Dimension VISTA (Siemens Healthcare Diagnostics, Eschborn, Germany) in SHIP-Start-2 and SHIP-Trend-0.

Statistical Analysis

Data documentation and statistical analyses were performed using IBM SPSS Statistics (Versions 23 - 25 for Windows) and SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Demographics of the study population are reported as medians with first and third quartiles or proportions. Duct diameters in the examined subgroups, i.e. with and without secretin and for selected age groups are given as medians with interquartile range. In multivariable quantile regression models, the relation of age, sex, BMI and alanine aminotransferase (ALAT) activity and median CBD or PD diameters was assessed. From these regression models the beta-coefficients, 95% confidence intervals and the p-values are reported. Moreover, the associations between BMI and ALAT with median CBD and PD diameters were visualized in scatterplots together with the original measured values.

Wilcoxon-Mann Whitney tests were used to inspect differences in native CBD and PD diameters between men and women and to inspect differences between healthy subjects and those with cholecystectomy. Duct diameters before and after secretin administration were compared using Wilcoxon signed rank sum tests. Statistical significance was assumed at a p value of ≤ .01 if not stated otherwise.

Age-dependent upper limits of normal duct diameters were determined with non-parametric quantile regression.[10] We defined the 95th percentile as upper limit of normal and determined respective normative values for each single year of age. Subsequently, upper limits of normal for the whole cohort, for subjects < 65 years and subjects ≥ 65 years as well as according to age decades were calculated and reported. Additionally, we illustrated the upper limits of

normal for the CBD and PD diameter together with the median, the original measured values and the conventional upper limit of normal in scatterplots. In a sensitivity analysis upper limits of normal were recalculated after exclusion of subjects who died, were lost-to-follow-up or who had developed incident pancreatic cancer or liver lesions.

Reliability of MRI readings was assured by analyzing intra-class correlation (ICC) using two-way mixed effect models testing for consistency for inter-rater reliability and absolute agreement for intra-rater reliability. ICC and Cronbach´s alpha above .8 were considered acceptable [11].

Beyer G, *et al. Gut* 2023; 72:1738–1744. doi: 10.1136/gutjnl-2021-326106

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Suppl. Table 1: Characteristics of the excluded subjects

Characteristics	Exclusions n=115
Male, %	47.8
Reason for exclusion*	
Cholecystolithiasis or choledocholithiasis	47
Chronic pancreatitis	14
Cystic pancreatic lesions	52
Acute/chronic liver disease**	14
Previous pancreatic or liver resection	0
Tumors of upper abdomen	0
Age, years	63.0 (55.0 - 70.0)
BMI, kg/m²	27.5 (25.2 - 30.2)
ALAT, µktatal/l	0.38 (0.29 - 0.55)
ASAT, µktatal/l	0.32 (0.27 - 0.41)
GGT, µktatal/l	0.52 (0.38 - 0.79)

Data are proportions or median (1^{st}-3^{rd} quartile). ALAT: alanine aminotransferase, ASAT: aspartate aminotransferase, BMI: body mass index, GGT: gamma-glutamyltransferase. *Some subjects harbored multiple multiple pathologies leading to exclusion. **defined as either intrahepatic cholestasis, liver cirrhosis or previous acute or chronic hepatitis

Suppl. Table 2: Results from multivariable quantile regression models assessing the effects of sex, age, BMI and ALAT on median native and secretin-stimulated CBD and PD diameters. ß-coefficients with 95% confidence intervals (CI) and p-values for an increase in one year (age), one kg/m² (BMI) and 0.1 µkatal/l are given.

Outcome	Exposure	ß (95% CI)	p
CBD native	sex (male vs female)	0.691 (0.438; 0.943)	< .001
	age (increase 1 year)	0.042 (0.034; 0.050)	< .001
	BMI (increase 1 kg/m²)	-0.023 (-0.044; -0.003)	.028
	ALAT (increase 0.1 µkatal/l)	0.015 (-0.040; 0.069)	.602
CBD secretin	sex (male vs female)	0.791 (0.545; 1.036)	< .001
	age (increase 1 year)	0.046 (0.038; 0.055)	< .001
	BMI (increase 1 kg/m²)	-0.017 (-0.044; 0.009)	.195
	ALAT (increase 0.1 µkatal/l)	0.021 (-0.033; 0.075)	.451
PD native	sex (male vs female)	-0.042 (-0.146; 0.062)	.425
	age (increase 1 year)	0.022 (0.018; 0.026)	< .001
	BMI (increase 1 kg/m²)	-0.018 (-0.029; -0.006)	< .01
	ALAT (increase 0.1 µkatal/l)	0.033 (0.011; 0.055)	< .01
PD secretin	sex (male vs female)	0.094 (-0.039; 0.226)	.167
	age (increase 1 year)	0.024 (0.020; 0.029)	< .001
	BMI (increase 1 kg/m²)	-0.019 (-0.033; -0.005)	< .01
	ALAT (increase 0.1 µkatal/l)	0.018 (-0.019; 0.054)	.348

CBD, common bile duct; PD, pancreatic duct; BMI, body mass index, ALAT, alanin aminotransferase

Beyer G, *et al. Gut* 2023; 72:1738–1744. doi: 10.1136/gutjnl-2021-326106

Suppl. Table 3: Upper reference limits for common bile duct (CBD) and pancreatic duct (PD) diameters in healthy subjects according to age in decades and administration of secretin

Age group, years	CBD		PD	
	native	secretin	native	secretin
<30	6.3	6.0	2.6	2.7
30-39	7.2	6.9	2.9	3.1
40-49	8.1	7.8	3.2	3.5
50-59	9.0	8.7	3.5	3.9
60-69	9.9	9.6	3.8	4.3
≥70	11.4	11.0	4.3	4.8

CBD: common bile duct, CCE: cholecystectomy, PD: pancreatic duct.

Beyer G, *et al. Gut* 2023; 72:1738–1744. doi: 10.1136/gutjnl-2021-326106

Suppl. Table 4: Sensitivity analysis - upper reference limits for common bile duct (CBD) and pancreatic duct (PD) diameters according to age, administration of secretin and cholecystectomy status (CCE).

CBD		**Upper limits of normal**		
		All ages	< 65 years	≥ 65 years
native	Healthy	9.1	8.0	10.9
	CCE	13.5	13.3	14.0
secretin	Healthy	8.8	7.6	10.8
	CCE	13.0	13.0	12.6
PD				
native	Healthy	3.6	3.2	4.2
	CCE	3.8	3.8	3.9
secretin	Healthy	3.8	3.4	4.5
	CCE	4.0	3.5	4.0

CBD: common bile duct, CCE: cholecystectomy, PD: pancreatic duct.

Beyer G, *et al. Gut* 2023; 72:1738–1744. doi: 10.1136/gutjnl-2021-326106

Suppl. Table 5: Inter- and intra-rater reliability

Reliability statistics	Inter-rater reliability of FK and PT		Intra-reader reliability of FK
	CBD	PD	
Cronbach's Alpha	0.954	0.983	0.939
Cronbach's Alpha for standardized items	0.954	0.984	0.939
Number of items	2	2	2
Intra-class correlation (95 % CI)			
single	0.912 (0.846 - 0.950)	0.967 (0.943 - 0.981)	0.884 (0.805 - 0.933)
mean	0.954 (0.917 - 0.975)	0.983 (0.970 - 0.990)	0.939 (0.892 - 0.965)

CI: confidence interval; CBD; common bile duct; PD: pancreatic duct

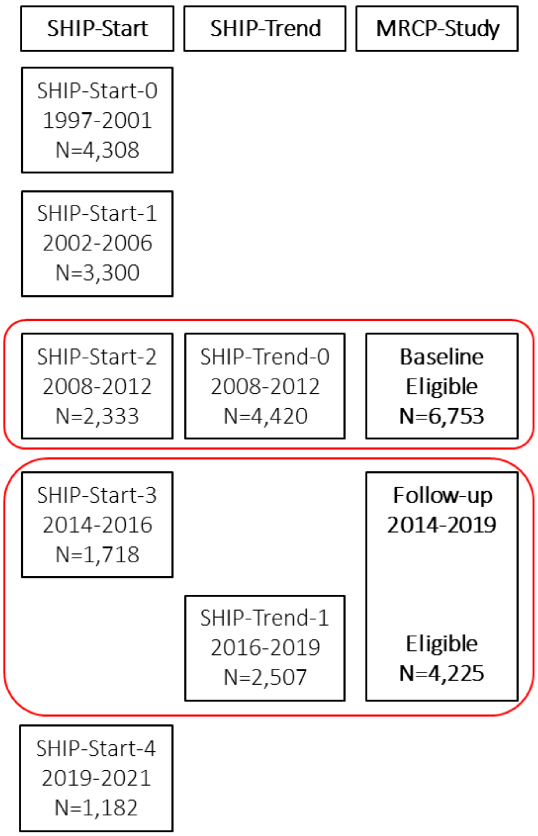
Beyer G, *et al. Gut* 2023; 72:1738–1744. doi: 10.1136/gutjnl-2021-326106

Suppl. Table 6: Overview on previous cohort studies

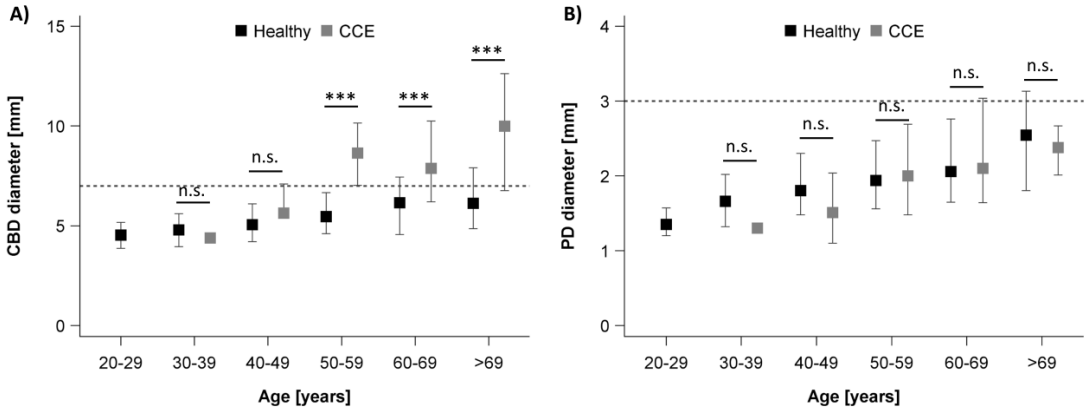
Study author	Modality	N	Median Age	CBD in mm	PD in mm	Increase with age	Increase with CCE	New reference limit
Govindan et al (2021) [12]	MRCP	517	54.6	5.4±1.4	/			8 mm
Karamanos et al. (2016) [13]	MRCP/ERCP	1.000	40.7	1.5-16.4	/			/
Peng et al. (2015) [14]	MRCP	862	46.10	4.13±1.11	/		/	/
McArthur et al. (2014) [15]	CT	304	51.9	5.07	/			/
Benjaminov et al. (2013) [16]	EUS	647	60.8	4.4-6.0	/			/
Chen et al. (2012) [17]	MRCP	187	51	4.6±1.8	/		/	/
Itoi et al. (2012) [18]	US	8840	51.6	4.5 ±1.4	/		/	2.83 + 0.03 x age
Senturk et al. (2012) [19]	CT	604	49.2	4.77±1.81	/			8mm for age > 50 years, 10 mm post-CCE
McArthur et al. (2012) [20]	US	720	50.9	3.5, post-CCE 4.5	/			
Park et al. (2009) [21]	CT	398	54.4	6.70±2.41	/		/	7mm for age > 50 years
Chawla et al. (2009) [22]	CT	80	53	5.2, post-CCE 6.9	/			/
Bachar et al. (2003) [23]	US	251	52.5	4.28±1.18	/		/	8,5 mm in elderly
Horrow et al. (2001) [24]	US	258	55	3.5±1.2	/		/	/
Kaim et al. (1998) [25]	US	92	84.7	6.2, post-CCE 8.7	/			10mm for age > 75 years, post-CCE 14mm
Feng und Song	US	234	/	5.9, post-CCE 6.1	/	/		/

(1994) [26]								
Wu, Ho und Chen (1984) [27]	US	203	21 to 60	3.3 – 6.8	/		/	/
Niederau et al. (1983) [28]	US	830	/	2.8 ±2	/			/
Frøkjær et al. (2020) [29]	MRCP	262	52.7		2 – 3 mm		/	2.7 mm for age > 60 years
Wang et al. (2019) [30]	MRCP	280	54.4		1.99±0.53		/	/
Testoni et al. (2009) [31]	MRCP	25	57.8	/	1.1±0.6	/	/	/
Glaser und Stienecker (1999) [32]	US	131	52	/	1.9		/	/
Hastier et al. (1998) [33]	ERCP	155	>70 vs <50	/	5.3 vs. 3.3		/	/
Anand et al. (1989) [34]	ERCP	55	36.9	/	3.3±0.91		/	/
Bolondi et al. (1984) [35]	US	18	26	/	1.2±0.4		/	/
Sivak und Sullivan (1976) [36]	ERCP	35		/	3.2±0.1		/	/

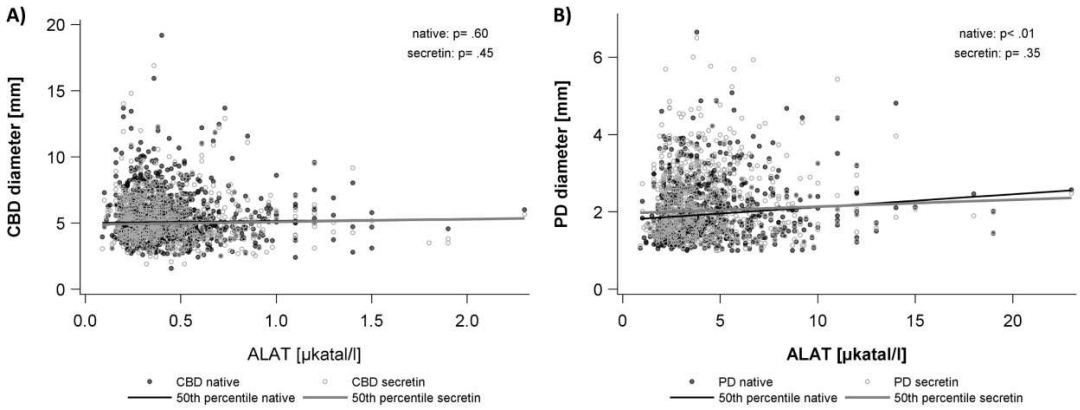
positive association
no association
/ not assessed



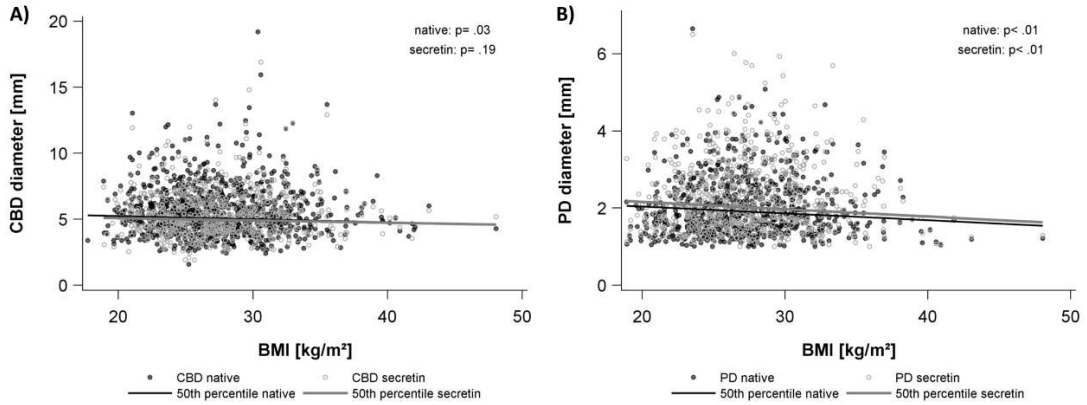
Suppl. Figure 1. Flow-chart and time line of the SHIP study cohorts from which the data included in the current analysis has been extracted.



Suppl. Figure 2. Median native duct diameters with 1.-3. quartile by age decade in healthy subjects and in subjects with cholecystectomy (CCE). The horizontal dotted line represents the conventional upper limit of normal of 7 mm and 3 mm for the respective duct. A) The diameter of the common bile duct (CBD) increases with age. CCE leads to a further increase in the diameter of the CBD. B) The diameter of the pancreatic duct (PD) increases with age. CCE has no impact on the diameter of the PD. Group differences between healthy subjects and those with CCE were tested with Wilcoxon-Mann Whitney tests. *** $p < .001$



Suppl. Figure 3. Scatterplot of the largest perpendicular diameter of (A) the common bile duct (CBD) and (B) the pancreatic duct (PD) according to alanine aminotransferase (ALAT) in healthy subjects. Solid lines represent the estimated 50th percentile as estimated from quantile regression models adjusted for sex, age and body mass index. Black dots and lines represent native duct diameters, grey dots and lines represent duct diameters after secretin administration on magnetic resonance cholangiopancreatography.



Suppl. Figure 4. Scatterplot of the largest perpendicular diameter of (A) the common bile duct (CBD) and (B) the pancreatic duct (PD) according to body mass index (BMI) in healthy subjects. Solid lines represent the estimated 50th percentile as estimated from quantile regression models adjusted for sex, age and alanine aminotransferase. Black dots and lines represent native duct diameters, grey dots and lines represent duct diameters after secretin administration on magnetic resonance cholangiopancreatography.